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AUTO-IMMUNE DISEASE

I. MODERN IMMUNOLOGICAL CONCEPTS*

BY

Sir MACFARLANE BURNET, O.M., M.D., F.R.S.

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Medicine has been the mother of all the biological sciences. There are many reasons for this, but one of them is specially relevant to my present topic. It is simply that while the body functions smoothly things are taken for granted. It is only when things go wrong that it becomes possible to perceive that there is something in normal function which requires understanding. The central theme of these lectures is that the phenomena seen clinically in diseases of the so-called auto-immune group can be interpreted to throw light on the nature of immunological processes, and equally that recent developments in theoretical immunology are becoming highly relevant to clinical medicine.

We were all taught to regard antibody production and other immune responses as manifestations of a process of defence against invading micro-organisms or any other type of foreign material entering the tissues. In some way the body was enabled to recognize what was foreign and to swing into action the immunological responses needed to speed its removal. The meaning of foreignness was something that seemed to worry nobody. Only with the recognition that there are disease conditions in which antibody is actually directed against body components—acquired haemolytic anaemia, for instance—did a real sense of the importance of the body's ability to differentiate between self and not self come into being.

In Melbourne I am closely associated with our Clinical Research Unit, but only as an immunological consultant without clinical responsibility. My approach to the medical problems must necessarily be at the theoretical level, but at the present time I believe that it is better to try to present a working approach to generalization about the auto-immune diseases than to add to the volume of clinical descriptions and therapeutic trials. The approach will be based very largely on a concept of immunity which is still a heterodox one—although it has some distinguished proponents—which has been called the clonal selection theory (Burnet, 1959). The stimulus to adopt such a theory came largely from a consideration of the pathology of immunity, and perhaps its chief virtue over earlier theories is its direct relevance to the problems of auto-immune disease.

The Facts of Immunity

Every human being has an immunological individuality that differentiates him from every other person—with only the minor qualification that identical twins are identical immunologically as well as in all other inheritable qualities. The most familiar evidence of this is the failure of a skin graft from another person to take, although autologous transfer of skin from one site to another on the patient is a standard technique.

These differences between individuals are of genetic origin, and one can express the basis of individuality as depending on two general concepts : (1) the chemical pattern of all the macromolecules of the body is genetically determined ; and (2) random gene mutation will introduce possibilities for discontinuous changes in macromolecular pattern, many of which will have no relevance for survival but will introduce immunological differences.

When foreign and hence potentially dangerous material enters the body—classically as an invading micro-organism—it requires to be recognized as foreign ; this recognition can only be based upon the fact that the alien material carries some molecular patterns which are not represented in the host. The classical immune responses obviously represent evolutionary adaptations needed to allow survival in a world teeming with potentially pathogenic micro-organisms. Equally obviously, any body component must not provoke the appearance of antibody or of cells which can react specifically to contact with it. Any defence force must know how to distinguish friend from enemy. The characteristic feature of what might be called the new immunology is its interest in the nature of the process by which this recognition of the difference between what is self and what is not self is mediated.

The possibility must not be excluded that some types of foreign material are so different from any found in a vertebrate body that other principles of recognition may come into play—for example, inability of body enzymes to break down certain chemical configurations.

There are several types of experimental material which bear on such differences. Skin-transplantation experiments in animals, usually mice, of known genetic constitution have been basic, but a variety of other types of transplantation, notably of malignant tumours and of bone-marrow suspensions, have also been used. Three findings from observations on cattle will provide a good introduction to the experimental approach.

1. If we take two randomly chosen calves and transfer pieces of skin from one site to another, we find that, as in human beings, autologous grafts will take place, while homologous grafts are rejected. When a graft from A is placed on B there is an initial phase during which the graft

*The first of two Croonian Lectures delivered before the Royal College of Physicians of London on June 16 and 18, 1959.

becomes vascularized, but within two weeks the graft area becomes inflamed and the foreign skin is rejected. If a second A to B graft is now tested the rejection is greatly accelerated. B has been modified by the experience of the first graft and is, as it were, immune to A, a phenomenon referred to as homograft immunity.

2. Calf twins are common enough, but identical twins are rare. If a pair can be found they will allow cross-transplantation. Grafts of A skin will take happily on B, and vice versa. This same mutual tolerance is observable in human identical twins, and depends on the genetic identity of the two subjects. With pure-line mice bred for many generations by brother-sister matings, genetic identity or near identity will also allow mutual tolerance of skin grafts.

3. It is well known that cattle twins usually develop a common placental circulation even when they are derived from two separate fertilized ova. When the sexes are different, hormonal interchange during embryonic life results in the female becoming a sterile "free-martin." If non-identical bovine twins are used for reciprocal skin grafts, takes occur as regularly as in identical twins (Anderson *et al.*, 1951). This is quite at variance with the findings in human beings, but it does call to mind a phenomenon observed earlier by Owen (1945) in such bovine twins—namely, that the pair would commonly show a sharing of two red blood cell groups between them. The two phenomena allow the formulation of an important provisional generalization—that cells present through embryonic life may persist into adulthood and be recognized as "self" even if they carry patterns genetically distinct from those of the other cells of the body.

The next step, due to Medawar and his colleagues (Billingham *et al.*, 1956), was to analyse the phenomena at the experimental level, using specially bred homozygous strains of mice. In discussing it I shall simplify the situation greatly and will gloss over the difficulties that made the results not as easily reproducible as could be wished. We have two strains of mice, A and B, A having white skin, B black. As proof of homozygosity, any A mouse will accept a graft from any other A mouse, the same holding for strain B. Grafts from A to B, or B to A, fail, and repeated homografts give rise to accelerated rejection—homograft immunity.

To imitate what happens in bovine twins, we can inoculate foetuses of A during the last week *in utero* with cells from strain B—for example, spleen or bone-marrow cells from adult B mice. After birth these mice treated *in utero* are found in a high proportion to accept a homograft of opposite type. It is possible to simplify matters by inoculating baby mice intravenously with the opposite type cells on the first day of life and still obtain the same tolerance of the homograft. We should be definite that when mouse A acquires tolerance for skin B it still retains its power to reject skin from strains C, D, and E. The effect is immunologically specific, and has been named by Medawar, "specific immune tolerance."

As I have hinted, the experiment is not always easy to accomplish, and two modifications may be mentioned which indicate the nature of some of the difficulties.

Suppose we have a mouse A rendered tolerant to B and carrying a healthy patch of black skin on its white coat. We transfer to this mouse lymph-node cells from a normal non-tolerant A mouse. They are accepted, and in a week or two the previously stable black graft begins to break down and is eventually rejected. The process can be accelerated if, instead of using a normal A mouse, we take the lymph node from an A mouse which has developed homograft immunity against B. It is clear that some capacity has been *lost* by the tolerant mice which can be replaced by cells from normal or immunized animals.

I have spoken of A and B strains of mice as if any pair of strains would serve. Actually they have to be chosen rather carefully. If we take, for instance, strains B and C and inoculate spleen cells of C into newborn B, we find that the baby B mice fail to flourish, most develop diarrhoea and die within three weeks, and an occasional stunted specimen will survive and can be shown to be tolerant to C skin. This has been called "runt disease" or secondary disease, and has been ascribed, with what seems to be excellent reason, to the immunological attack of the *graft* on the host. The strongest evidence for this interpretation is that by using *embryonic* C cells tolerance can be induced without runt disease. Here we have a process by which two sets of embryonic tissues can both become tolerant of the foreignness of the other.

So far we have been concerned with situations in which tolerance or immunity is provoked by living cells from the same species of animal but of a different strain. Presumably these reactions are produced because of chemical differences between the strains in some of their cellular proteins or other macromolecules. The next step then is to find whether pure proteins foreign to the body can behave in similar fashion. We know that they can produce antibody when inoculated into grown animals, and in recent years several workers have produced a non-responsive state by administration of such antigens to very young animals.

Behaviour of Foreign Proteins

Smith and Bridges's (1958) studies of bovine serum albumin (B.S.A.) in rabbits inoculated on the first day of life have provided a relatively simple picture. If 100 mg. is administered the rabbit will fail to respond by antibody production to any further injection of that antigen for something over three months. If, however, the delay before testing extends for 200 days or more the second injection will provoke an antibody rise. By a study of the relation between size and dose and the time over which non-responsiveness to antibody extended, Smith and Bridges concluded that the effect of the first injection is to induce a state of non-responsiveness which persisted only so long as some of the foreign antigen was present in the body. By appropriate timing it was possible to maintain a rabbit quite inert to B.S.A., although reacting normally to any unrelated antigen. Smith and Bridges believe that their results indicate that tolerance in Medawar's sense is dependent on the continued persistence of the relevant antigens.

From all these observations it is clear that the adult animal can differentiate in some way between substances which have been present in the body since some stage of embryonic or neonatal life and substances foreign to the body. Everything indicates that this capacity for recognition is a function of the cells characteristically present in spleen and lymph nodes. It is a function of some or all of the mesenchymal cells of the body.

Our immediate problem is to find the best working hypothesis which will cover these facts and provide a basis for the phenomena from human disease that I shall consider in the second lecture.

Let us start from Smith and Bridges's data on B.S.A. In the non-responsive rabbit B.S.A. can be differentiated

(by this fact of non-reactivity) from a variety of other antigens, presumably from all other antigens not very closely related to B.S.A. B.S.A. is, in fact, treated as if it were part of the rabbit's own albumin—it is eliminated at the same rate, and by all tests is immunologically quite inert as long as tolerance lasts. Broadly speaking, there are only two possible mechanisms by which the differentiation of B.S.A. from other foreign antigens could be achieved. Antibody is produced by cells, and we can ascribe failure to produce an antibody despite presence of the normal stimulus to one or other of two alternatives: (1) the preparatory injection at birth may have inhibited or eliminated a set of cells (or clones of cells) which alone are capable of producing antibody against B.S.A.; or (2) if cells capable of producing one antibody can, under corresponding circumstances, produce any other antibody, then the preparatory injection must modify one region in all such cells while leaving many other regions available for reaction with other antigens.

Either interpretation, as well as any conceivable compromise or alternative, demands a very extensive store of "information" which in some way or another must be stored in the mesenchymal cells. "Information" is used here in a technical sense, which, however, is not very far from its normal one. So far we have been concerned only with experimental situations in which a foreign antigen or group of antigens has been used to trick the body into recognizing it as self; but, without attempting to elaborate the point, we can be equally certain that the same holds for all the multitude of potentially antigenic materials and chemical configurations to be found amongst the normal components of the body. None of them provoke antibody production, presumably because of a process equivalent to the production of tolerance to foreign cells. A particularly cogent example concerns the rare blood group "Bombay." Here there is a genetic block which prevents the production of any of the ABO antigens in the body. In their absence anti-A and anti-B and anti-H (O) agglutinins develop in the serum (Bhende *et al.*, 1952). In normal individuals, of course, one or more of the antigens are present and the corresponding antibodies are never produced.

We may state the first requirement of any comprehensive immunological theory, that it will account for the fact that *from the time of birth there is in the body an adequate supply of information to allow the recognition of vast numbers of antigenic configurations as either "self" or "not self."*

There are many other aspects of immunity, but from our special interest in auto-immune disease this is clearly the most important, just as in the earlier discussions of immunology it was probably the most neglected. Very briefly, the other important features of immunological phenomena to be considered are:

1. The specific complementary relationship of antigen and antibody on which all methods of demonstrating antibody depend.

2. The difference between primary and secondary types of immune response.

3. The existence of three qualitatively distinct types of immune response which can often be evoked by the same antigen—classical antibody production, "hay-fever type" antibody production, and delayed hypersensitivity.

4. The long persistence of immunological memory in the sense, for example, that an injection of tetanus toxoid will give a secondary type response in a man whose last injection was 15 or 20 years previously—or that immunity to measles will last a lifetime without reinforcement by re-exposure to infection.

5. The development of delayed hypersensitivity and of effective immunity following virus disease in patients with congenital agammaglobulinaemia who cannot produce antibody.

Immunological Theories

This is not the place to discuss details of immunological theory beyond what is necessary to provide a framework of ideas against which to discuss immunopathology. The weakness of standard theories of antibody production is simply that they provide no point of approach to the problems of auto-immune disease. The clonal selection theory of immunity is still only something in the process of being shaped into usefulness. It has been fairly fully described at the experimental and theoretical level (Burnet, 1959), and only a summary account is given here.

Essentially, classical theory holds as self-evident that antigen entering the body as something completely foreign and unknown imprints its character on certain cells and enforces them to produce globulin molecules carrying a complementary pattern. This globulin, by uniting with the foreign material, may neutralize any toxic qualities it possesses and in general prepare the way for its accelerated elimination from the body. On classical theory the pattern of the antigen provides the information which is incorporated in the pattern of the antibody and makes it specifically reactive with the antigen. It is necessary to assume that, in addition to providing antibody pattern, antigen is also the stimulus which provokes the antibody-producing cells to proliferate and to synthesize and liberate antibody.

Clonal Selection

Clonal selection theory, on the other hand, allows the antigen no part in impressing pattern on the antibody-producing cell. The capacity to produce a given antibody is a genetically determined quality of certain clones of mesenchymal cells, the function of the antigen being to stimulate cells of these clones to proliferation and antibody production.

In these lectures I am concerned only with potential antigens which form part of the body, or which may be present in other individuals of the same or other vertebrate species. It does not necessarily follow that the concepts I am using are equally applicable to antigens that are completely remote from those of vertebrate tissues. It may be a fundamentally significant finding that with one slightly equivocal exception no one has demonstrated tolerance to a bacterial antigen.

Any biological theory will need *ad hoc* elaboration in various directions to cover the complications of reality, and this is no exception. The most important extension is to devise a way by which the information needed to differentiate between body components and foreign material can be derived—with at the back of our minds the need to have in reserve a possible interpretation for the breakdown in that "information service" in auto-immune disease.

The clonal selection approach is to generate a very large number of clones by allowing a high degree of somatic mutability in the early stages of embryonic development. If such mutation is at random many clones will be initiated which will correspond to potential antigenic determinants in the body. The central

feature of the hypothesis is that contact of immunologically competent cells with corresponding antigen during embryonic life results in the elimination of those cells. If the rate of mutation slows down sharply in the second half of embryonic life, this double process of mutation and elimination of clones corresponding to antigenic determinants in the body will automatically provide a range of residual clones capable of reacting with all foreign antigenic patterns. Figs. 1 and 2 may clarify this idea.

It is not wholly an *ad hoc* assumption that an immunologically competent cell, if embryonic, will react with the corresponding antigenic determinant and be destroyed, while if adult it will be stimulated to proliferate. Antigen–antibody contact is capable of a variety of damaging effects in the body, and it is well known that excess antigen can inhibit antibody production in the immunologically mature animal.

If somatic mutation can modify immunological pattern at random, some way to eliminate cells which have undergone an unfortunate mutation must exist.

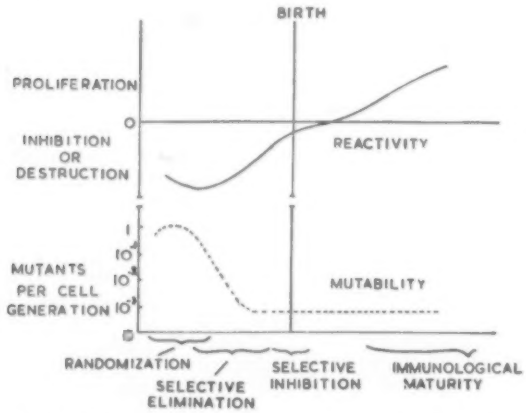

FIG. 1.—The essential features of the clonal selection theory. Above: The changing reactivity of an immunologically competent cell to contact with the corresponding antigenic determinant: before birth inhibition or destruction with gradual change; after birth to proliferation and antibody liberation. Below: Postulated mutability of the relevant portion of the genome, at first so high as to be virtually a process of randomization.

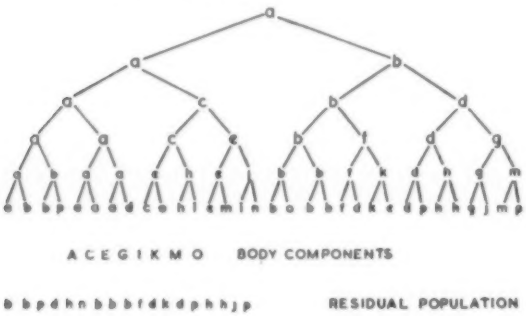

FIG. 2.—An attempt to illustrate how immunological information could be generated. Each lower-case letter indicates an immunological pattern (potential antibody) corresponding to an antigen shown by upper-case letter. If from the stabilized random population all patterns corresponding to body components are eliminated, the residual population will be able to react only with foreign configurations—that is, it will be able to recognize antigenic determinations as "not self."

Obviously if a mutant clone should arise which corresponds immunologically to a determinant in, say, the serum albumin molecule, it must be eliminated rather than fostered. A simple hypothesis which will provide such a homoeostatic mechanism is to assume that once a cell has been stimulated to proliferate by an antigenic stimulus it will pass through a transient phase in which it is susceptible to destruction or inhibition on further contact with the same antigenic determinant. Whenever the antigenic determinant is freely present in the body and accessible to the corresponding immunologically competent cells, such destructive contacts would be inevitable. So far as one can judge, the recorded data on the reaction of animals to very large amounts of antigen contain nothing incompatible with such an hypothesis. On the other hand, there is, strictly speaking, no positive experimental evidence either of somatic mutation of the type postulated or for this type of homoeostasis. With the rapid development of the experimental approach to cellular immunology both problems should, however, soon come within the range of experimental decision.

Cells Involved

The discussion so far has made no specific reference to the cells involved beyond the fact that they are of mesenchymal origin. The interrelationships of these cells and the correlations between morphological appearance and function are still controversial. There is, however, sufficient convergence of view to allow some general remarks to be made. In the first place, some of the studies on the repopulation of bone marrow and lymphoid tissue after *x*-irradiation and treatment with heterologous cells (Ford *et al.*, 1957) point very strongly to a unitarian origin of the whole group of mesenchymal cells, including granulocytic and erythrocytic series. The various determinants involved in the changes from one morphological form to another are almost completely unknown, but there is no doubt that such changes do occur. Within the range of cells, which include reticulum cell, large, medium, and small lymphocyte, plasma cell, macrophage, and fibroblast, almost every possible interconversion has been described. In any clonal approach it will be necessary to accept the possibility that within an immunologically competent clone representative cells may have the morphological appearance of any of the standard types.

On any interpretation the small lymphocyte must play an important part as the commonest of all mesenchymal cell types. Probably the most significant thing about the lymphocyte is its scant amount of cytoplasm in comparison with the nucleus, with the obvious suggestion that the nucleus is the significantly functional portion of the cell. A nucleus contains two things that may be important—genetic information and nucleic acids. Many have suggested that the lymphocyte might be a convenient means of bringing the building blocks required for nucleic acid synthesis to a given region of the body. Alternatively, one could regard the lymphocyte as a carrier of the information needed to allow it to transform into a functioning cell of more than one type, the cytoplasm being limited to functioning merely as support for various trigger mechanisms that will set such transformations in action. This is very much in line with the views of Yoffey, Farr, and others, but a majority of histologists would probably still consider the lymphocyte an end-cell. It is still only a hypothesis —but it is a good hypothesis pointing to many types

of experimental approach—that the main function of the lymphocyte is the carriage of immunological information.

The other cell type that requires discussion is the macrophage. Despite the prominence that was once given to cells of the reticulo-endothelial system in theories of antibody production, the present trend is to deny them any such function. Macrophages take up antigen but they do not produce antibody. There have been theories that a first stage of antibody synthesis takes place in the macrophage, the product then being transferred to a cell of the lymphoid series. There is, however, neither experimental evidence nor theoretical necessity for such an assumption. Modern work, such as, for example, that of Uhr, Salvin, and Pappenheimer (1957), points to the effectiveness of minute amounts of antigen as a stimulus, and it may well be that the main function of the macrophage is not to collect antigen in order to make antibody but to reduce the concentration of antigen to a level which will not embarrass the antibody-producing cells.

All workers are agreed that the production of antibody is a function of plasma cells and that the characteristic morphology of a plasma cell is no more than evidence that it is in fact actively synthesizing and liberating protein. Since the monograph of Fagraeus (1948) there has been no serious doubt on this point, but the final proof that plasma cells produce antibody was only provided last year by Nossal (1959) in Melbourne. He showed that plasma cells from an immune animal when isolated in microdrops as single cells produced antibody, while small lymphocytes from the same lymph-node suspension did not.

At the cellular level, the essence of the clonal selection theory is that contact of antigenic determinant with immunologically competent cells—presumably lymphocytes—can stimulate them in various ways: (*a*) to liberate pharmacologically active agents such as histamine and serotonin, and perhaps (*b*) to be rendered non-viable in the process; (*c*) to proliferate, producing more cells of the lymphoid series; and (*d*) to give rise to antibody-producing plasma cells. The type of response will depend on (1) the physiological state of the cell, (2) the concentration of the antigen, and (3) the site in which the stimulated cell lodges.

To those who have not been in touch with recent developments in immunology this may well seem a paradoxical and unconvincing way of looking at a phenomenon which has a much more straightforward interpretation. There are still many immunologists who would prefer the Haurowitz–Pauling hypothesis in one or another elaboration. On this view the antigen or its effective portion is retained in the antibody-producing cell, where it acts as the template against which each antibody molecule is synthesized. Unfortunately this is a point of view that makes no contact whatever with the phenomena of tolerance and of immuno-pathology. The clonal selection theory that I have presented will certainly have to be modified in the light of the experimental studies that it has already stimulated, and it may eventually be discarded, but any new theory or rehabilitation of an old one will have to have equal relevance to these key phenomena.

A Recapitulation

Let me in conclusion recapitulate this theory. Its major difference from earlier theories is its contention that the antigen does not determine the pattern, the specificity of the antibody, in any more direct sense than the giraffe's habit of browsing on tree leaves has lengthened its neck. It is a Darwinian, not a Lamarckian, approach.

Perhaps we can put the difference between the two into modern terms. It is a "central dogma" of modern biochemical genetics that only genetic processes can modify the information in a genetic system. There is no presently conceivable way by which information from the environment can be incorporated into the nucleic acid of the chromosomes. The flow of information is always from the genetic to the biochemical, never in the opposite direction. The chain of command is pictured as deoxyribonucleic acid—ribonucleic acid protein (D.N.A.—R.N.A.—protein), and on this dogma there is no way in which an antigen can meaningfully influence the pattern of D.N.A.

To satisfy these requirements we have introduced the concept of a hypermutable segment of the genome in mesenchymal cells, especially during the early stages of differentiation. It is of interest that detailed study of bacteriophage mutability shows "hot spots" where mutations are much more frequent than at other loci (Stent, 1958). It is not unreasonable to believe, therefore, that the needs of survival might have led to the evolution of a "hot spot" of this type in the genome of mesenchymal cells. This allows the postulate that all conceivable patterns which can be taken by the rather small specific area of antibody globulin molecules could be represented in the genomes of cell clones arising in the course of embryonic life. Tolerance results from the elimination or inhibition of all cell clones which react with antigenic determinants present in the body.

Immediately after birth the body begins to make contact with antigens of all sorts, notably bacterial antigens derived from the alimentary canal. This initiates a process that continues through life. When antibody is needed it is automatically produced by specific stimulation of the cells in clones preadapted to react with the corresponding antigenic determinants. When the antigen disappears from the body the proliferative stimulus lapses and the clones slowly diminish in importance. Mutational change will also in most cases gradually erase the specific character of the clones unless some natural or artificial "booster" is encountered. So that by adult life the immunological experience of the body is incorporated not only in the antibodies that are circulating in the blood but in the clones of cells that make up the cell populations of spleen, lymph nodes, bone marrow, and the various local accumulations of lymphoid tissue.

From the point of view of human pathology, the great virtue of the clonal selection approach is its provision of a basis for the emergence of antibody or of immunologically active cells directed against body components. Almost all who have discussed the character of such a disease as acquired haemolytic anaemia are clear that the anomaly is not in the red cells which are damaged but in the cells which produce the abnormally reactive globulins found in the plasma. It is an essential feature of our hypothesis that mutation in immunological pattern is always in process. Random mutation is bound to produce a proportion of patterns reactive against body components, and in the normal individual there must be a mechanism by which cell clones of such character are prevented from

proliferating. It is convenient to refer to such clones and the immunological patterns they carry as "forbidden" clones or "forbidden" patterns, and to regard the mechanism by which they are eliminated as part of the general homoeostatic control of body structure and function.

A wide variety of medical conditions in the body represent the partial failure of homoeostatic mechanisms—auto-immune disease can be interpreted best as another example of partial and often temporary failure of one such mechanism. Instead of being eliminated certain forbidden clones of cells find opportunity to proliferate and, in reacting with the antigen involved, inflict damage on the body.

REFERENCES

Anderson, D., Billingham, R. E., Lampkin, G. H., and Medawar, P. B. (1951). *Heredity*, **5**, 379.
Bhende, Y. M., Deshpande, C. K., Bhatia, H. M., Sanger, R., Race, R. R., Morgan, W. T. J., and Watkins, W. M. (1952). *Lancet*, **1**, 903.
Billingham, R. E., Brent, L., and Medawar, P. B. (1956). *Phil. Trans. B*, **239**, 357.
Burnet, F. M. (1959). *The Clonal Selection Theory of Acquired Immunity*. Cambridge Univ. Press, England, and Vanderbilt Univ. Press, Nashville, Tennessee.
Fagraeus, A. (1948). *Acta med. scand.*, Suppl. 204.
Ford, C. E., Ilberry, P. L. T., and Loutit, J. F. (1957). *J. cell. comp. Physiol.*, **50**, Suppl. 1, p. 109.
Nossal, G. J. V. (1959). In press.
Owen, R. D. (1945). *Science*, **102**, 400.
Smith, R. T., and Bridges, R. A. (1958). *J. exp. Med.*, **108**, 227.
Stent, G. S. (1958). *Nature (Lond.)*, **182**, 1769.
Uhr, J. W., Salvin, S. B., and Pappenheimer, A. M. (1957). *J. exp. Med.*, **105**, 11.

[*The second Croonian Lecture will appear in next week's issue.*]

EXPERIMENTAL STUDY OF AN ERYTHROPOIETIC PRINCIPLE PRODUCED IN THE KIDNEY

BY

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The present paper is concerned with problems related to erythropoiesis. An attempt is made to extend our knowledge of the mechanism regulating the level of erythrocytes in the body, and to throw light on the pathogenesis of some types of anaemia. Special attention is given to anaemia developing in the uraemic condition.

Anaemia occurs in most types of human renal insufficiency. This form of anaemia, like that of chronic infection, appears to be due both to a reduction of the life-span of the red cell and to deficient marrow response (Wintrobe, 1956). That author states: "It has been repeatedly noted, however, that the rate of corpuscular elimination has not been such that it could not be met by increased production, were erythropoiesis accelerated to the full capacity of the bone marrow. It is noteworthy that erythropoiesis in the bone marrow may not be reduced below the normal, and, although there is usually no increase in reticulocytes, an occasional normoblast may be found in the blood smear. Nevertheless, red cell production does not accelerate sufficiently to meet the demand." The cause of the anaemia, however, in renal disease, as well as in chronic infection, hepatic disorder, hormonal disturbance, neoplastic disease, etc., is still obscure.

In the experiments young male mice of the WLO (White Label, Oslo) strain were used. A great number of the animals were rendered nephritic by local *x*-ray irradiation of the kidneys, done under ether anaesthesia. During the irradiation the whole animal was shielded with lead, with the exception of the exteriorized kidney, which was hanging down in a plastic chamber through which Ringer's solution at 37° C. was flowing. The physical data were: 50 kV, 2 mA, hvl 0.3 mm. Al. The distance from focus to mid-axis of the kidney was 31 mm. The dose rate was about 1,700 r/min. An even dose distribution was obtained by irradiation from both sides.

Reticulocytes were counted in Nile-blue Giemsa-stained blood smears; 2,000 cells were counted on each slide. As an immediate reticulocyte response of short duration may be regarded as an outflow of reticulocytes not related to cell production (unpublished personal material), only protracted reticulocytosis of several days' duration has been used as an indicator of red-cell production. The haemoglobin value was measured by means of Ljungberg's colorimeter. Blood-urea values were determined in all nephritic and some of the normal animals by means of a gas volumetric method (Horn, 1951). In some of the animals, erythrocytes, haematocrit, and CO_2-combining power ("alkali reserve") (Roughton and Scholander, 1943; Scholander and Roughton, 1943: Scholander *et al.*, 1947) were determined. With exception of the reticulocyte values, only a few of the results of these laboratory investigations are reported here: they are presented in the accompanying charts. To indicate the variation between the observations, ± 1 standard deviation has been calculated, and plotted in the graphs.

Evidence that an Erythropoietic Principle is Produced in the Kidney

The anaemia developing in uraemic mice with irradiated kidneys was found to vary from hypochromic to normochromic. Generally the reticulocyte count was slightly lower in the uraemic than in the normal mice. With increasing blood nitrogen accumulation, the bone marrow showed a hypoplastic erythropoiesis.

During a study, begun in 1956, on functional and anatomical changes in mice produced by *x*-ray irradiation of the exteriorized kidneys, the following observations were made: (1) By irradiation of the kidneys in mice a condition resembling the essential features of glomerulonephritis in man was produced. (2) In mice with total irradiated kidneys a definite but slight decrease in the haemoglobin values was noted, with only slight rise of the blood urea. (3) After unilateral nephrectomy alone, the blood urea rose from the normal 20 mg. per 100 ml. to about 30, and on removing one kidney and half of the other the blood urea rose to about 50 mg. per 100 ml. These animals, however, had only a mild, transient anaemia in spite of their raised blood urea. (4) In mice in which a small amount of kidney tissue was shielded during the irradiation, it was possible to produce uraemia with a blood-urea value about 150 mg. per 100 ml. without anaemia (Osnes, 1958).

These observations led to the following conclusions: The failure of the kidney as an excretory organ and the development of anaemia are parallel phenomena and independent of each other. These findings also indicate that the kidney may produce a principle of importance in erythropoiesis, and lack of this principle

may be the cause of the anaemia developing in *x*-irradiated nephritic mice.

In the animals, mentioned above, with partial nephrectomy or partial irradiated kidneys, normal kidney tissue functioning as an excretory organ was present. It may be disputed whether a uraemic intoxication in such a condition is the same as when all the excretory kidney tissue is involved in disease.

As a further test to show that the kidney produces an erythropoietic principle the following experiments were done:

Three groups of mice were irradiated with 8,000 r on the *left* kidney. In group A the right kidney was removed (control group). In group B the ureter of the right kidney was ligated. In group C a peritoneal outlet from the ureter of the right kidney was made. It will be observed that the right kidney in groups B and C was no real excretory organ because of the ligation of the ureter (group B), or because the urine produced was reabsorbed from the peritoneal cavity (group C). Excretion of urine to the urinary bladder was possible only from the left irradiated kidney in all groups, but the excretory function was so impaired as to produce a marked uraemia in all of them. The average blood-urea value in groups A, B, and C seven weeks after irradiation was 156, 152, and 160 mg. per 100 ml. respectively. The average haemoglobin value seven weeks after irradiation was 46.5% in group A, 66.3% in group B, and 99% in group C (Fig. 1).

The question is, what is the reason for the difference in the haemoglobin values in these cases? If we postulate production of an erythropoietic principle by the kidney tissue, it may be supposed that the left

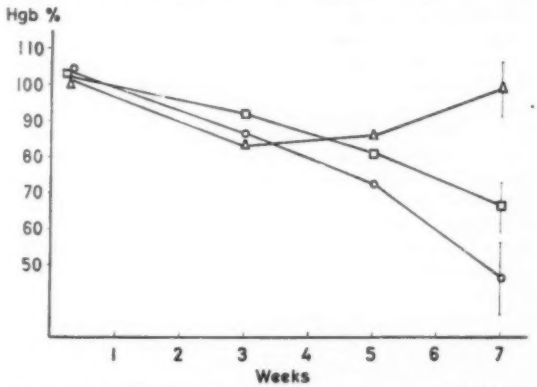

FIG. 1.—Haemoglobin values in mice with *x*-irradiated left kidney (8,000 r). A, Right kidney removed (17): O—O. B, Right ureter ligated (14): □—□. C, Right ureter peritoneal outlet (6): △—△.

irradiated kidney produces the same amount of this principle in all groups. In group A, with the right kidney removed, only the left irradiated kidney could produce this postulated erythropoietic principle. In group B hydronephrosis of the right kidney developed, with partial destruction of the kidney tissue, and a postulated endocrine function might be impaired in this kidney. In group C, however, there was no destruction of the right kidney at all; on the contrary, a marked hypertrophy was observed. If the kidney produces (or activates) any principle of importance in erythropoiesis it may be expected that this function would be intact in this non-irradiated kidney.

In accordance with this, a progressive anaemia developed in group A. In group B an anaemia also developed, but to a lesser degree. In group C an initial anaemia was observed, but later the haemoglobin value increased to nearly normal. The initial anaemia observed in the latter group might be caused by a transitory non-bacterial infection (ureo-peritonitis).

The results of this experiment clearly indicate that the kidney produces (or activates) a principle of importance for the erythropoiesis, and that *x*-ray irradiation of the kidney impairs the production of this principle. Beside

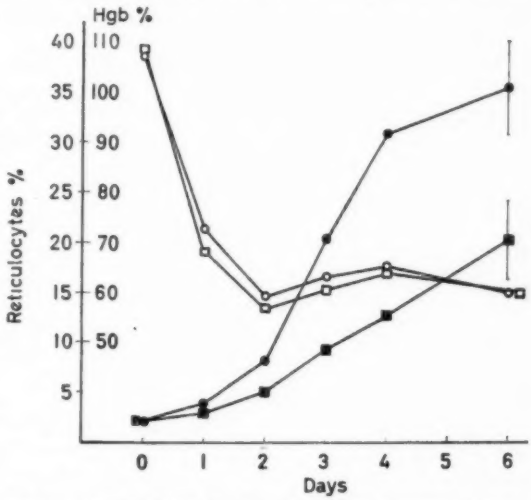

FIG. 2.—Haemoglobin values and reticulocyte response. Normal bled mice (6): ○—○, Hb; ●—●, reticulocytes. Partially nephrectomized bled mice (6): □—□, Hb; ■—■, reticulocytes.

this, the experiment shows that retention of toxic products does not necessarily impair erythropoiesis.

These findings are consistent with the following experiments. Fig. 2 shows the haemoglobin value and the reticulocyte response after daily bleeding in mice with intact kidneys, and in mice with partial nephrectomy, only half a kidney being left intact. With the same degree of anaemia in the two groups, the reticulocyte response in animals which had one kidney and half of the other removed was only about one-half of that in the group with intact kidneys. This result is in accordance with the interpretation that a reduction in the mass of kidney tissue implies a reduction in the amount of kidney factor available.

Fig. 3 shows the reticulocyte response in three groups of mice bled to the same degree (0.5 ml.). In group A both ureters were ligated. In group B both kidneys

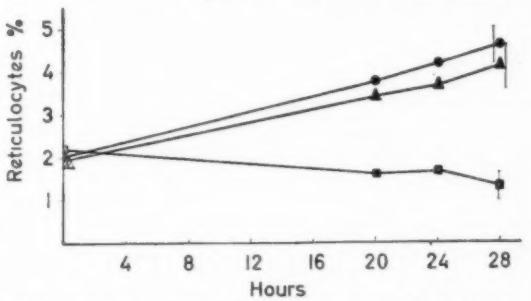

FIG. 3.—Reticulocyte response in 3 groups of mice bled 0.5 ml. A, Ureter-ligated bled mice (6): ●—●. B, Nephrectomized bled mice (6): ■—■. C, Nephrectomized bled mice treated with activated serum (6): ▲—▲.

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were removed. In group C both kidneys were removed and the animals were treated with a single injection (2% of body weight) of serum from bled mice ("activated" serum). A good reticulocyte response is seen in animals with ligated ureters (group A), but no reticulocyte response in animals with kidneys removed (group B), in agreement with the findings of Jacobson *et al.* (1957). Group C, however, with kidneys removed, followed by injection of activated serum, shows good reticulocyte response. The average blood-urea levels in these groups 28 hours after intervention were 335, 339, and 332 mg. per 100 ml. respectively. The average haemoglobin values were 70, 71, and 73.3% respectively. The life span after intervention varied from 28 to 40 hours in all groups.

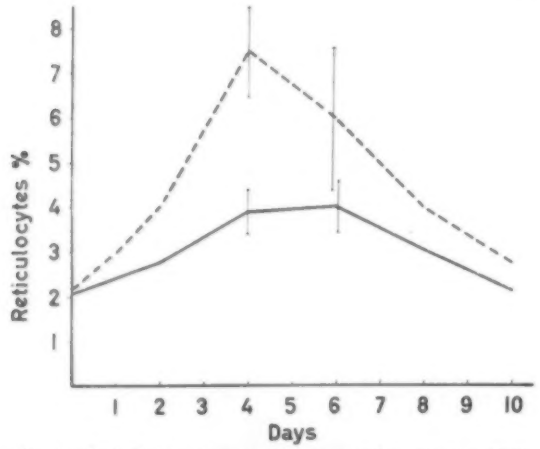

FIG. 4.—Reticulocyte response of normal mice and of nephritic mice treated with one injection of activated serum. Donors: Bled mice. Recipients: ——, normal mice (5); - - - -, nephritic mice (6).

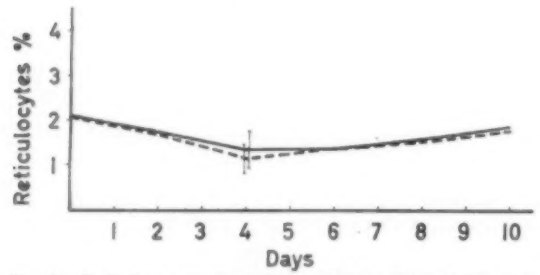

FIG. 5.—Reticulocyte response of normal mice and nephritic mice given one injection of normal serum. Donors: normal mice. Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

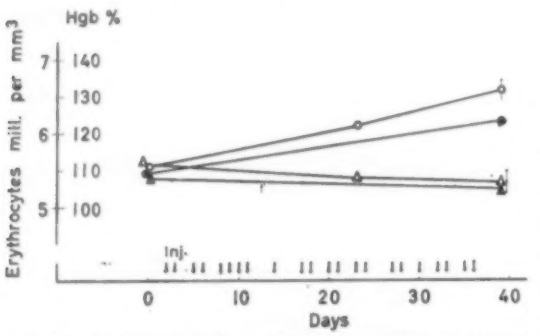

FIG. 6.—Haemoglobin values and red-cell counts. A, Normal mice treated with activated serum (6): ○——○, Hb; ●——●, erythrocytes. B, Normal mice treated with normal serum (6): △——△, Hb; ▲——▲, erythrocytes.

The fact that ureter-ligated animals react with reticulocytosis after bleeding, whereas the nephrectomized animals do not, might indicate that the latter were in a condition unable to react with reticulocytosis. The fact, however, that the nephrectomized animals were able to respond to a substance present in serum from bled mice shows the opposite to be true.

These latter experiments agree well with the findings demonstrated in Fig. 1, and corroborate the conclusion that the kidneys produce a principle of importance in erythropoiesis.

Studies on Erythropoiesis-stimulating Substances in Serum from Mice

Carnot and Deflandre (1906) have discussed a factor in plasma capable of stimulating erythropoiesis. Since this observation was made a considerable literature, presenting rather divergent views on the subject, has grown up. Problems related to erythropoiesis have been reviewed by Grant and Root (1952), Erslev (1955), and Jacobs (1958).

The fact that anaemic serum injected into an animal may cause marked erythropoiesis points to a regulating factor in the blood. Many authors have dealt with the isolation of erythropoiesis-stimulating factors. No one, however, has been able to determine the chemical nature of the erythropoiesis-stimulating substances. The nature of the stimulus for secretion of the erythropoietic principle is uncertain, and opinions about which is the tissue of origin are controversial and without firm foundations. Villa and Sala (1937) suggested that a reticulocytosic factor was formed in the liver. These authors were able to demonstrate such a factor in blood from the liver vein in rats, but not in blood from the liver artery or the portal vein. Jacobson *et al.* (1958) found that cobaltous chloride administration, acute haemorrhage, and hypoxic hypoxia after bilateral nephrectomy fail to elevate plasma erythropoietin, whereas bilateral ureter ligation reduces but does not eliminate the rise of plasma erythropoietin. They concluded that the kidney may be the site of erythropoietin production. These authors, however, point out that they cannot state with certainty that a negative response obtained by use of their methods of assay indicates the absence of erythropoietin(s) from the plasma or plasma extracts investigated; and they add that perhaps the kidney may not be involved in erythropoietin(s) production at all.

The term *erythropoietin* is used in this paper to describe a principle found in serum capable of stimulating erythropoiesis when injected into a *normal* organism.

Fig. 4 shows the reticulocyte response in a group of normal mice and in a group of nephritic mice treated with a single injection (2% of body weight) of activated serum. The donor mice were rendered anaemic by bleeding two days in succession (to a haemoglobin value about 40%), and on the third day serum from these animals was given to the two recipient groups. A very good reticulocyte response was observed in normal as well as in nephritic recipients, reaching a maximum about the fourth day, and with a duration of about 10 days.

Fig. 5 shows a parallel experiment where normal and nephritic mice were injected with serum from normal unbled mice. This serum caused no reticulocytosis in the recipient groups; on the contrary, a depression of the reticulocyte values was observed in normal as well as in nephritic mice.

A rise of the reticulocyte values in the blood does not necessarily mean an increased production of red blood cells. In long-term experiments, however, repeated injections (each 0.3 to 0.4 ml.) of activated serum into normal mice (Fig. 6) were followed by a rise in haemoglobin values from 111 to 131.7% and a rise in red-cell count from 5.47 to 6.16 millions/c.mm., whereas the administration of normal serum in the same amounts caused a decrease in haemoglobin values as well as in red-cell counts. In accordance with these findings, the reticulocytosis observed in normal mice after injection of activated serum (Fig. 4) may be regarded as an indication of increased red-cell production.

Fig. 7 shows the haemoglobin values and the body weights in two groups of nephritic mice in which each kidney had been exposed to 4,000 r. At 75 days after *x*-ray irradiation the haemoglobin value, the body weight, and the condition of the animals were about the same in both groups. In group A repeated injections of activated serum (each 0.35 ml.) were started 79 days after irradiation. Group B (control group) was not treated with serum at all, because administration of protein to mice in a nephritic state of this degree had been found to be badly tolerated generally, whereas activated serum could be injected with caution. It is seen that progressive anaemia could be prevented by injections of activated serum, and that with closer-spaced injections the haemoglobin value finally increased. During the experiment the serum-treated animals (group A) showed only a slight decrease of the body weight, and by the end of the experiment they were in a much better condition than the animals in the untreated group. The average blood-urea value was 62 mg./100 ml. in group A, against 114.5 mg. in group B. The average kidney weight was 249 mg. in group A, against 190 mg. in group B. The average heart weight was 140.6 mg. in group A, against 149.2 mg. in group B.

These experiments are promising also with regard to the treatment of human nephritis. As mentioned above, an increased protein load in a nephritic animal usually lowers its condition. We observed that the animals receiving activated serum not only became less anaemic but their general condition, including the uraemia, improved.

Fig. 8 shows the reticulocyte response in a group of normal mice and in a group of nephritic mice treated with a single injection (2% of body weight) of serum from nephritic mice. The serum donors with irradiated kidneys had haemoglobin values ranging from 30 to 68%. Fig. 8 shows that these nephritic donors also possessed substances in their serum able to produce reticulocytosis in normal mice (erythropoietin), but no demonstrable amounts of substances producing reticulocytosis in nephritic recipients. This experiment clearly demonstrates that the substance(s) producing reticulocytosis in normal mice and the substance(s) producing reticulocytosis in nephritic mice must be different.

Fig. 9 shows a similar experiment, but here the serum donors were nephrectomized and bled mice kept alive by means of intermittent peritoneal lavage (Grollman *et al.*, 1951). The serum transfusion was done 50 hours after nephrectomy and bleeding. The serum from these nephrectomized bled mice contained substances producing reticulocytosis in normal mice (erythropoietin) but no traceable amounts of substances producing reticulocytosis in nephritic mice. This observation does not agree with the findings of Jacobson *et al.* (1958) that there is no rise in the erythropoietin titre after bleeding in nephrectomized animals. The present experiment shows that the erythropoietin production can go on in the absence of the kidneys, and it must be concluded that the erythropoietin *per se*, as defined above, is produced outside the kidney.

Fig. 10 shows the reticulocyte response in nephritic mice treated with a single injection (2% of body weight) of serum from bilateral ureter-ligated and bled mice.

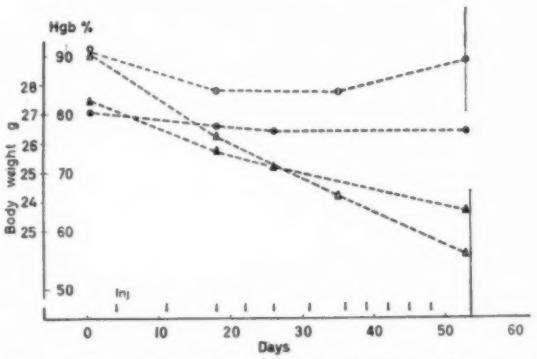

FIG. 7.—Haemoglobin values and body weights in mice exposed to 4,000 r. A, Nephritic mice treated with activated serum (7): ○---○, Hb; ●---●, body weight. B, Nephritic mice not treated (6): △---△, Hb; ▲---▲, body weight.

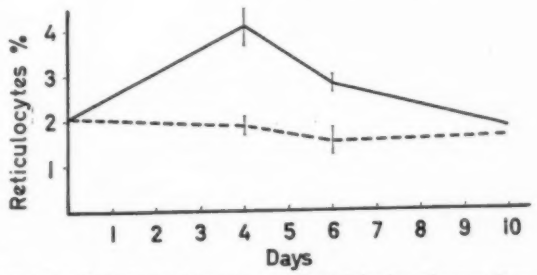

FIG. 8.—Reticulocyte response to a single injection of serum from nephritic mice. Recipients: ——, normal mice (6); - - - -, nephritic mice (4).

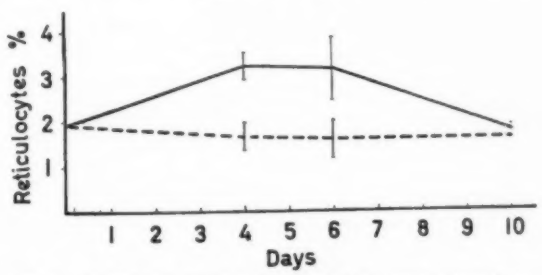

FIG. 9.—Reticulocyte response to a single injection of serum from nephrectomized bled mice. Donors: Nephrectomized bled mice. Recipients: ——, normal mice (6); - - - -, nephritic mice (4).

As in the former experiment, the donors were kept alive by means of intermittent peritoneal lavage. The serum transfusion was done 46 hours after ligation of the ureters and bleeding. This serum was able to produce reticulocytosis in nephritic mice, and thus the serum from ureter-ligated bled mice (as well as the serum from normal bled mice, Fig. 4) contained an erythropoietic principle which is not found either in nephritic anaemic mice (as shown in Fig. 8) or in nephrectomized bled mice (Fig. 10). In accordance with the findings already demonstrated it may be concluded that this erythropoietic principle, which is different from erythropoietin, is produced (or activated) in the kidney, and the lack of this principle may be the cause of the anaemia developing in *x*-rayed nephritic mice.

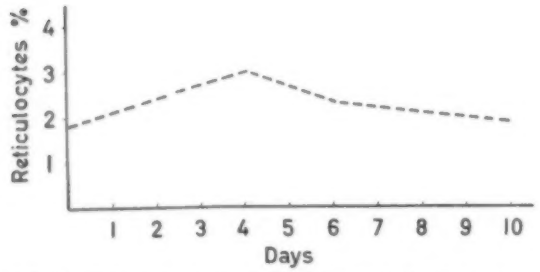

Fig. 10.—Reticulocyte response of nephritic mice to one injection of serum from bilateral ureter-ligated bled mice. Donors: Ureter-ligated bled mice. Recipients: ----, nephritic mice (3).

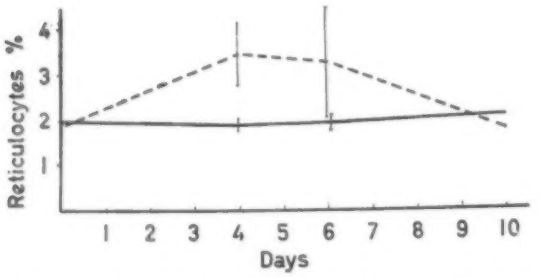

Fig. 11.—Mice treated with ultrafiltrate of activated serum. Recipients: ——, normal mice (6); ----, nephritic mice (6).

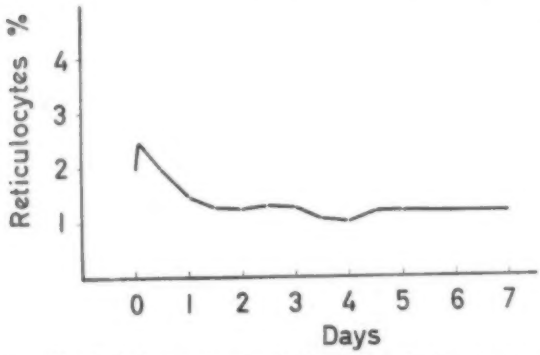

Fig. 12.—Reticulocyte response in six cordotomized bled mice.

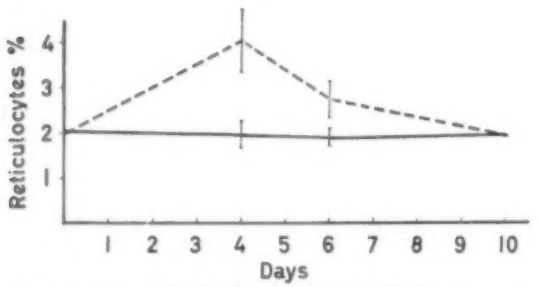

Fig. 13.—Donors: Cordotomized bled mice. Recipients: ——, normal mice (6); ----, nephritic mice (4).

In order to characterize the active principles discussed above, an ultrafiltrate of activated serum was injected into normal and nephritic mice (Fig. 11). The ultrafiltration was made at 2–4° C. in the course of about 28 hours. The recipients received a single injection (2% of body weight). This protein-free filtrate produced reticulocytosis in nephritic mice, but not in normal mice. This observation supports the idea that erythropoietin may be a protein or a protein-bound substance, whereas the principle producing reticulocytosis in nephritic mice is not a protein.

This active protein-free ultrafiltrate, treated in a boiling-water bath for three minutes, injected in the same dose as mentioned above, did not give rise to reticulocytosis in nephritic recipients. This shows that the erythropoietic principle produced in the kidney may be thermolabile.

In accordance with the experiments presented above, erythropoietin, as well as the erythropoietic principle produced in the kidney, may be regarded as necessary for the production of erythrocytes. As demonstrated in Figs. 8 and 9 the principle (erythropoietin) producing reticulocytosis in normal mice does not produce reticulocytosis in nephritic mice (nephritic mice themselves have raised erythropoietin titre—Fig. 8), and, vice versa, the principle producing reticulocytosis in nephritic mice (the erythropoietic principle formed in the kidney) does not produce reticulocytosis in normal mice (Fig. 11). By means of recipient groups of normal and nephritic animals we have a biological means of testing a serum with regard to these two different erythropoiesis-stimulating principles.

A very interesting problem is how the secretion of these active principles is regulated in the body. Hayashida and Ueno (1936, 1937) found no reticulocytosis after acute haemorrhage in rabbits with the spinal cord cut above Th. 2. Such animals, however, were able to respond to serum from normal bled rabbits with reticulocytosis. Serum from normal unbled rabbits, and serum from bled rabbits with cut spinal cord, produced no reticulocytosis when injected into rabbits with cut spinal cord. These findings indicate a nervous regulation of some erythropoiesis-stimulating principle. Hayashida (1936) tried to localize blood-regulating centres in the brain, and was of the opinion that such a centre existed in the area surrounding the tuber cinereum.

In accordance with the findings of Hayashida and Ueno, we obtained no reticulocyte response in a group of six mice which had the spinal cord cut at the level of C. 6 and were bled (Fig. 12). During the operation the animals were anaesthetized under ether for five minutes. Apart from a slight rise immediately after the operation, the reticulocyte values were found to be decreased.

Sera from cordotomized bled mice were tested in a group of normal and a group of nephritic mice (Fig. 13). The serum transfusion was performed 60 to 72

hours after cordotomy and bleeding. The recipients received a single injection of the serum (2% of body weight). No reticulocyte response was seen in the normal mice (no erythropoietin effect), whereas the response in the nephritic mice was pronounced (effect of the principle produced in the kidney). This indicates that the secretion of erythropoietin may be regulated by a central nervous mechanism through the spinal cord, whereas the secretion of the principle produced in the kidney is not. It is assumed that all nerve connexions from the brain and the brain stem to the kidneys are destroyed by cutting the spinal cord at the level of C. 6 (vagal nervous fibres to the kidney have never been demonstrated: Smith, 1951), and therefore the secretion of the erythropoietic principle produced in the kidney is probably not subject to nervous regulation at all. This is in close agreement with the successful homotransplantation of the human kidney between identical twins (Murray *et al.*, 1958). It is likely that the regulation of the erythropoietic principle produced in the kidney is humoral.

It has been suggested that the erythropoietic principle produced in the kidney is connected with the granules of the juxtaglomerular cells (Osnes, 1958). Further experiments (to be published) on the regulation of the kidney factor corroborate this view.

Studies on Erythropoiesis-stimulating Substances in Human Serum

Müller (1912) injected serum from anaemic guinea-pigs into bled mice. He found that the blood values of the mice did not fall at the rate shown in control experiments, and thus demonstrated that the species barriers could be crossed with respect to an erythropoietic principle. Loeschcke and Schwartzer (1939) and Schwartzer and Loeschcke (1940) injected serum into rabbits from newborn infants, and found a rise of the blood values of the animals. Since then serum from human beings with haematological disorders has been tested for erythropoietin by a number of investigators. In most of the anaemic patients investigated, as well as in cases of polycythaemia vera, a raised erythropoietin titre has been found. According to the majority of investigators, lack of erythropoietin does not seem to be a cause of anaemia in man.

It is of great interest to test human serum in *nephritic* mice in order to determine if lack of the erythropoietic principle produced in the kidney may be responsible for any type of human anaemia. Sera from 12 patients have been tested so far. Most of the sera were from patients with anaemia refractory to treatment. In each of the experiments one group of normal mice and one group of nephritic mice were given a single injection (2% of body weight) of human serum. The reticulocytes were counted before injection and 4, 6, and 10 days after.

Fig. 14 shows that injection of normal human serum caused a depression of the reticulocytes in normal as well as in nephritic mice, in accordance with the findings after injection of serum from normal mice (Fig. 5). This does not imply that erythropoietin and the erythropoietic principle produced in the kidney are not present in normal serum, but the amount of these substances may be too small to produce an effect discernible with the technique applied. Why the injection of normal serum causes a depression of the reticulocytes is uncertain. Steinberg *et al.* (1958) found that the maturation of bone marrow was suppressed by multiple injections of bovine and human serum into rabbits, and attributed this to the presence of specific factors in the serum inhibiting the erythropoiesis.

Figs. 15 and 16 show the reticulocyte response in normal and nephritic mice after injection of human serum from one patient with severe haemorrhage and one with sideropenic anaemia respectively. These sera produced reticulocytosis in normal as well as in nephritic mice corresponding to the findings after injection of serum from bled mice (Fig. 4). From these observations it may be assumed that both the titre of erythropoietin and the titre of the erythropoietic principle produced in the kidney usually increase in the anaemic subject—that is, if the anaemia is not to be ascribed to lack of one of these principles.

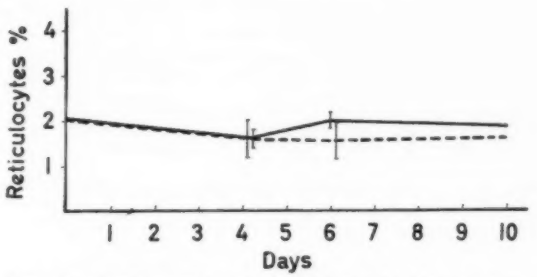

FIG. 14.—Findings after injection of normal human serum. Human donor (neurasthenia cordis; Hb 104%). Recipients: ——, normal mice (6); - - - -, nephritic mice (5).

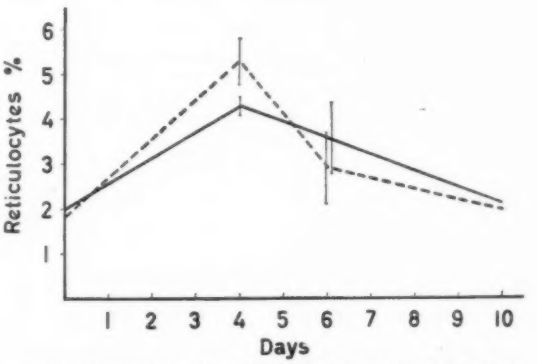

FIG. 15.—Human donor (anaemia posthaemorrhagica (Mb. Osler); Hb 27%). Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

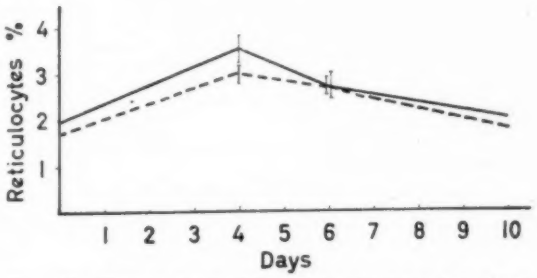

FIG. 16.—Human donor (sideropenic anaemia; Hb 53%). Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

Figs. 17 and 18 show the reticulocyte response in normal and nephritic mice after injection of serum from anaemic patients suffering from chronic nephritis. These sera produced reticulocytosis in normal but not in nephritic mice, in accordance with the findings after injection of serum from *x*-irradiated nephritic mice (Fig. 8). These findings indicate that lack of the erythropoietic principle produced in the kidney may be the cause of the anaemia which accompanies chronic nephritis in man, and the pathogenesis of the anaemia may be the same in *x*-irradiated nephritic mice and in human nephritis.

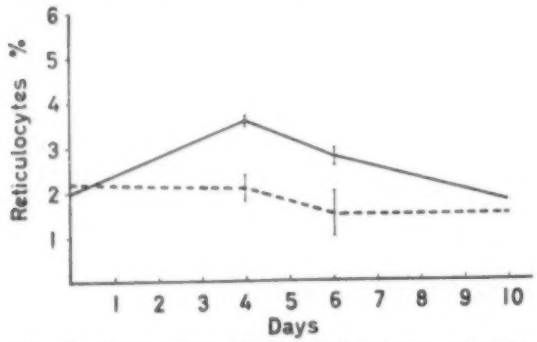

FIG. 17.—Human donor (chronic pyelonephritis; Hb 59%). Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

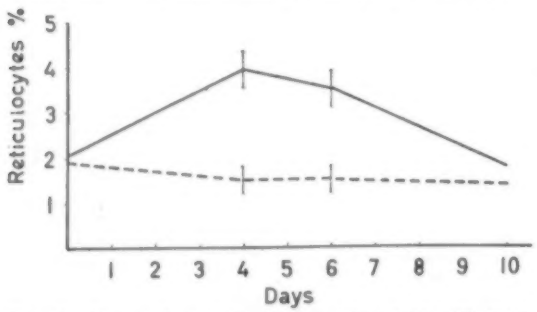

FIG. 18.—Human donor (chronic glomerulonephritis; Hb 59%). Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

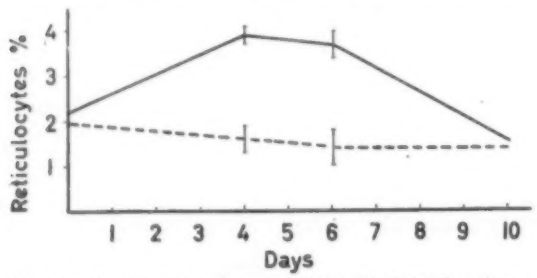

FIG. 19.—Human donor (ulcerative colitis; Hb 63%). Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

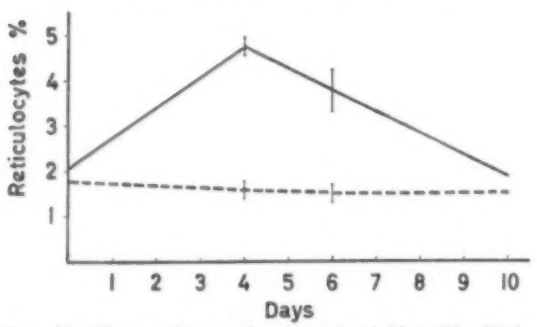

FIG. 20.—Human donor (chronic polyarthritis; Hb 63%). Recipients: ——, normal mice (6); - - - -, nephritic mice (5).

Figs. 19 and 20 show the reticulocyte response in normal and nephritic mice after injection of serum from anaemic patients suffering from chronic infection (ulcerative colitis, rheumatic arthritis). Normal mice responded with reticulocytosis, whereas nephritic mice did not. This is the same finding as after injection of serum from nephritic patients. Accordingly, it is suggested that some, if not all, the anaemias seen in chronic infection may be caused by lack of the erythropoietic principle produced in the kidney.

Figs. 21, 22, and 23 show the reticulocyte response after injection of serum from three patients with aplastic anaemia. Serum from two of these patients produced reticulocytosis in normal as well as in nephritic mice. Serum from the third patient, however, produced reticulocytosis in normal mice only. It is possible that the small amount of erythropoietic principle produced in the kidney was the cause of the anaemia in this patient. The apparent discrepancy underlines the possibility that these cases may differ with regard to pathogenesis.

Fig. 24 shows that injection of serum from a patient with polycythaemia caused reticulocytosis in normal but not in nephritic mice. This patient had also pyelo-ureteritis cystica and haematuria: the polycythaemia may be regarded as caused by the high erythropoietin titre.

In accordance with the results of the experiments with cordotomized mice (Fig. 13) the anaemia developing in man after lesions of the upper part of the spinal cord may be expected to be due to lack of erythropoietin. Such sera, however, have not yet been available for testing, but the results of testing the serum from a patient with chronic hepatitis are given in Fig. 25. No reticulocyte response was seen in the normal mice, whereas the response in the nephritic mice was marked. This indicates that the erythropoietin may be produced by the liver, and that the anaemia in hepatic disorders may be due to lack of erythropoietin.

The experiments presented in this section are pilot investigations of human sera in various haematological disorders. The number of investigations is too small to allow general conclusions. The results, however, are

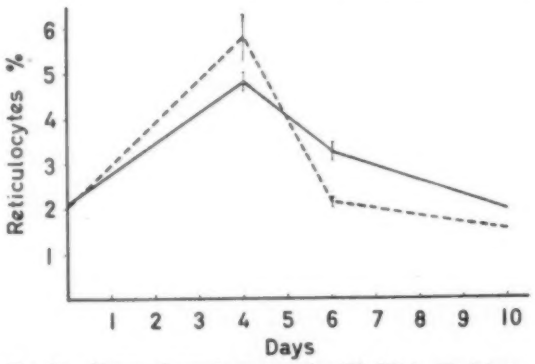

FIG. 21.—Human donor (pancytopenia; Hb 25%). Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

in accord with those described in the previous two sections, and give some information about the mechanism which regulates the haemoglobin value in the body.

Discussion

The production of erythrocytes is a complex process, and a great number of different substances are necessary for erythropoiesis, such as proteins, minerals, vitamins, hormones, etc. With exception of erythropoietin, all these substances seem to have a common property in that an increased supply of one of them does not raise the haemoglobin value over the normal level. As already pointed out, the erythropoietic principle produced in the kidney has not caused reticulocytosis in normal mice with the technique used. It is assumed that an increased supply of this principle does not increase erythrocyte production in the normal subject. For this reason the erythropoietic principle produced in the kidney is *not* termed erythropoietin. Erythropoietin, however, is able to increase the haemoglobin value above the normal level, but it may be a condition that all other substances necessary for erythropoiesis are present in sufficient amounts. Erythropoietin therefore may be a key substance in regulation of the haemoglobin level.

As demonstrated by some of the above experiments, the erythropoietin titre is prone to rise in anaemic conditions. If anaemia is caused by lack of some substance necessary for erythropoiesis (as iron, erythropoietic kidney principle, etc.), then erythrocyte production is impaired because of this lack, and sufficient red blood cells cannot be produced in spite of the increase in erythropoietin titre. Such a serum, rich in erythropoietin, accelerates erythropoiesis when injected into a normal subject having all substances necessary for erythrocyte production, but having *a priori* an erythropoietin titre stimulating only to normal erythrocyte production. This explains why serum from an anaemic organism, unable to heal its own anaemia, may produce reticulocytosis when injected into a normal subject.

If, however, the production of erythropoietin is itself impaired, as demonstrated in cordotomized bled mice and in one anaemic patient suffering from chronic hepatitis, it is not to be expected that such a serum will produce reticulocytosis when injected into a normal subject.

Work is in progress to isolate the erythropoietic principle produced in the kidney. If this substance becomes available we may be able to treat anaemias caused by the lack of it. The experiments on mice illustrated in Fig. 7 give us reason to hope, too, that an increase of haemoglobin values in anaemic patients with renal disease may counteract progression of the disease itself.

Summary

By means of experiments in mice (partial *x*-ray irradiation of the kidneys, performing peritoneal outlet from the ureter, ureter ligation, partial and total nephrectomy, as well as injections into mice of serum from mice treated in different ways and from human beings with various types of anaemia) it has been possible to demonstrate that the kidney produces a principle of importance in erythropoiesis.

This erythropoietic principle differs from erythropoietin. Secretion of the former can take place also when the connexions from the brain and the brain stem to the kidneys have been destroyed. The principle is ultrafilterable and has been found thermolabile.

Lack of this erythropoietic principle produced in the kidney is found to be the cause of the anaemia developing in *x*-rayed nephritic mice. By treatment of such mice with serum from normal bled mice which is rich in this principle, it has been possible to prevent the anaemia, and atrophy of the kidneys and the degree of uraemia were less in the serum-treated animals than in the controls.

Injection of serum from normal unbled mice into normal mice reduced the reticulocytes in the recipients;

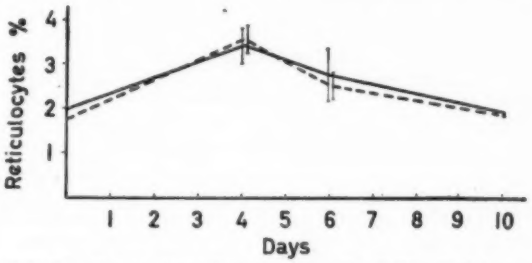

Fig. 22.—Human donor (pancytopenia; Hb 51%). Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

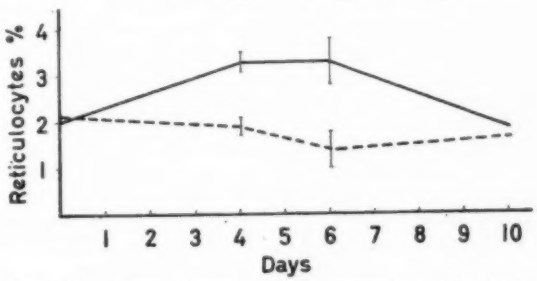

Fig. 23.—Human donor (aplastic anaemia; Hb 56%). Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

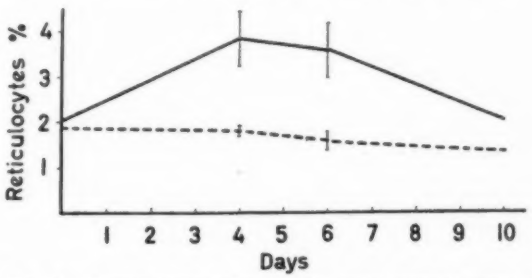

Fig. 24.—Human donor (polycythaemia; pyelo-urethritis cystica; Hb 98%). Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

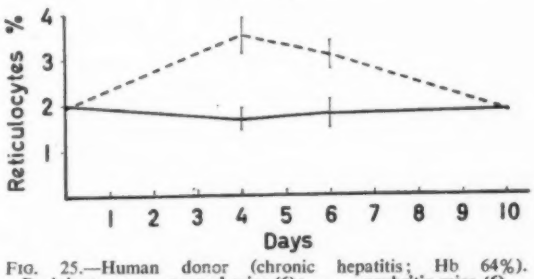

Fig. 25.—Human donor (chronic hepatitis; Hb 64%). Recipients: ——, normal mice (6); - - - -, nephritic mice (6).

continuance of injections caused a decrease in haemoglobin values as well as in red-cell counts.

Injection of serum from normal *bled* mice into normal mice caused reticulocytosis, and continued injections produced polycythaemia.

Erythropoietin produces reticulocytosis when injected into normal mice, but not in nephritic mice. The erythropoietic principle produced in the kidney, however, brings about reticulocytosis when injected into nephritic mice, but not in normal mice. From these findings it has been possible to test serum from mice as well as from human beings with regard to two different erythropoietic principles.

The titre of erythropoietin as well as that of the erythropoietic principle produced in the kidney generally increases in the anaemic patient, if the anaemia is not to be ascribed to lack of one of these principles.

No rise in the titre of the erythropoietic principle produced in the kidney has been found in anaemic patients suffering from chronic nephritis. This indicates that the lack of the erythropoietic principles produced in the kidney may be the cause of the anaemia accompanying nephritis in man.

No rise in the titre of the erythropoietic principle produced in the kidney has been found in anaemic patients suffering from chronic infection (ulcerative colitis, rheumatic arthritis). This finding has led to the conclusion that some, if not all, of the anaemias seen in chronic infections may be caused by the absence of the erythropoietic principle of the kidney.

Totally nephrectomized bled mice are able to increase their erythropoietin titre. This observation shows that erythropoietin is produced outside the kidney. No rise in the erythropoietin titre was found in a patient suffering from chronic hepatitis. This indicates that the erythropoietin is produced in the liver.

[ADDENDUM.—Since this paper was written sera from another five anaemic patients have been tested.

Serum from one patient suffering from pernicious anaemia gave, as expected, good reticulocyte response in normal as well as in nephritic mice (no lack of the two erythropoietic principles discussed in this paper). Serum from one patient suffering from chronic glomerulonephritis and sera from two patients suffering from chronic rheumatic infection gave good reticulocyte response in normal but no response in nephritic mice (lack of erythropoietic factor produced in the kidney). Serum from one patient suffering from chronic hepatitis gave no reticulocyte response in normal but good reticulocyte response in nephritic mice (lack of erythropoietin).

These results show complete agreement with the tests described in the paper above.]

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REFERENCES

Carnot, P., and Deflandre, C. (1906). *C.R. Acad. Sci. (Paris)*, **143**, 384.
Erslev, A. J. (1955). *Blood*, **10**, 954.
Grant, W. C., and Root, W. S. (1952). *Physiol. Rev.*, **32**, 449.
Grollman, A., Turner, L. B., and McLean, J. A. (1951). *A.M.A. Arch. intern. Med.*, **87**, 379.
Hayashida, M. (1936). *Kumamoto Igakkai Zasshi*, **12**, 1296.
—— and Ueno, T. (1936). Ibid., **12**, 1764.
—— —— (1937). Ibid., **13**, 1335.
Horn, L. (1951). *Scand. J. clin. Lab. Invest.*, **3**, 157.
Jacobs, M. H. (1958). *Ann. Rev. Physiol.*, **20**, 405.
Jacobson, L. O., Goldwasser, E., Fried, W., and Plzak, L. (1957). *Nature (Lond.)*, **179**, 633.
—— —— Gurney, C. W., Fried, W., and Plzak, L. (1958). Second United Nations International Conference on the Peaceful Uses of Atomic Energy. Paper No. 847.
Loeschcke, E., and Schwartzer, K. (1939). *Mschr. Kinderheilk.*, **81**, 25.
Müller, P. T. (1912). *Arch. Hyg. (Berl.)*, **75**, 290.
Murray, J. E., Merrill, J. P., and Harrison, J. H. (1958). *Ann. Surg.*, **148**, 343.
Osnes, S. (1958). *Brit. med. J.*, **2**, 1387.
Roughton, F. J. W., and Scholander, P. F. (1943). *J. biol. Chem.*, **148**, 541.
Scholander, P. F., Flemister, S. C., and Irving, L. (1947). Ibid., **169**, 173.
—— and Roughton, F. J. W. (1943). Ibid., **148**, 573.
Schwartzer, K., and Loeschcke, E. (1940). *Klin. Wschr.*, **19**, 64.
Smith, H. W. (1951). *The Kidney: Structure and Function in Health and Disease*. Oxford Univ. Press, New York.
Steinberg, B., Dietz, A. A., and Martin, R. A. (1958). *Lab. Invest.*, **7**, 458.
Villa, L., and Sala, A. (1937). *Klin. Wschr.*, **16**, 927.
Wintrobe, M. M. (1956). *Clinical Hematology*, 4th ed., p. 590. Kimpton, London.

NASAL STAPHYLOCOCCI AND SEPSIS IN HOSPITAL PATIENTS

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The noses of healthy individuals probably form by far the largest breeding-ground for the pathogenic staphylococci, and it is known that staphylococci from the nose can be responsible for septic lesions in the same individual. This has been shown for recurrent furunculosis (Valentine and Hall-Smith, 1952), for recurrent styes (Roodyn, 1954), and for minor industrial wounds (Williams and Miles, 1949). Studies of the incidence of cross-infection in one surgical ward at St. Bartholomew's Hospital have been in progress for the past three years, and a preliminary analysis (cited by Williams, 1958) suggested that nasal carriers of *Staphylococcus aureus* suffered wound infection more often than non-carriers. This analysis was therefore extended to the records from other wards.

Materials and Methods

The results described in this paper are derived from studies in three male surgical wards (A, B, and C) and one male medical ward (D). The analyses in the first half of the paper, on the nasal carrier state of 602 hospital patients, are based almost entirely on the records from ward A, while the analyses in the second half of the paper relating nasal carriage to sepsis are derived from the 1,358 patients in all four wards.

Ward A had 25 beds; we have already described the nursing regimen (Shooter *et al.*, 1958). Ward B was of the same shape and size as ward A and the nursing practices were similar. Ward C was similar physically, but differed in that no attempt was made to isolate patients with septic lesions. Ward D had 26 beds; again patients with sepsis were not isolated. Studies were carried out during the following periods. A: September, 1956, to May, 1957, and December, 1957, to September, 1958; B: May, 1958, to April, 1959; C: January to April, 1959; and D: October, 1958 to April, 1959.

Clinical records were kept of all wounds in the surgical wards. The term "septic" was used to denote the presence of visible pus. In both surgical and medical wards a note was made of the occurrence of other septic lesions—for example, boils, otitis media, chest and urinary infections, and enteritis. In this paper only septic lesions from which *Staph. aureus* was isolated are considered.

In all the wards nasal swabs were taken from the patients on admission or as soon after as convenient. Thereafter they were taken weekly. Swabs from noses and lesions were cultivated on blood-agar, and colonies resembling staphylococci were tested for coagulase production. All coagulase-positive strains were tested for phage-type by the routine described by Anderson and Williams (1956). No more than one colony from one culture was tested unless there were obvious colonial differences. In this paper the term "*Staph. aureus*" or just "staphylococci" is used to describe coagulase-positive strains.

Carrier Rates

Altogether 38% of the 602 patients admitted to ward A carried *Staph. aureus* in their nose during the first week after admission to hospital; 13% of them carried staphylococci resistant to penicillin. There was a steady increase in the general carrier rate for staphylococci and in the rate of resistant strains in patients swabbed during their stay in hospital, so that of the patients swabbed after eight weeks in hospital some 70% carried *Staph. aureus*. in the nose and half carried penicillin-resistant strains (Table I). It is clear from Table I

TABLE I.—*Nasal Carrier Rates for Staph. aureus During Stay in Ward*

Week	No. Patients	No. (and %) Carrying *Staph. aureus*		
		Penicillin-resistant	Penicillin-sensitive	Total
1	602	80 (13)	150 (25)	230 (38)
2	399	81 (20)	95 (24)	176 (44)
3	221	67 (30)	48 (22)	115 (52)
4	132	48 (36)	28 (21)	76 (58)
5	86	34 (40)	15 (17)	49 (57)
6	47	18 (38)	9 (19)	27 (57)
7	34	15 (44)	6 (18)	21 (62)
8	25	13 (52)	4 (16)	17 (68)
9	19	10 (53)	4 (21)	14 (74)
10	11	6	1	7
11	9	4	2	6
12	6	3	—	3
13	4	1	—	1
14	4	2	—	2

that the greater part of the increase in carrier rate could be accounted for simply by acquisition of penicillin-resistant staphylococci in the ward. Of the patients who were non-carriers on admission 30% had acquired resistant staphylococci by the third week in hospital, compared with only 18% of those who carried sensitive strains on admission (Table II).

TABLE II.—*Acquisition of Penicillin-resistant Staphylococci in the Nose*

Carrier State in First Week	No. of Patients	Cumulative Percentage* Acquiring Resistant Strains on or Before Week			
		2	3	4	5
No *Staph. aureus*	372	16	30	46	54
Penicillin-sensitive *Staph. aureus*	151	10	18	25	25

* Percentage calculated on life-table basis to give the proportion of original entrants who would be expected to have become carriers in the specified weeks, based on the experience of the patients then still in the ward.

Almost half of the 173 patients who had two or more positive nasal cultures showed a change in the drug sensitivity or in the phage type of the staphylococcus they carried. Of 30 patients whose staphylococci showed a change in penicillin sensitivity, only 3 appeared to have retained a staphylococcus of unchanged phage-type; 24 showed definite differences in the phage-pattern, 2 had untypable strains, and in 1 one of the strains was not tested for phage-type.

There were 353 patients who had two or more nasal swabs and who were not carrying penicillin-resistant strains in the first week (Table III); 98 acquired a

TABLE III.—*Acquisition of Penicillin-resistant Staphylococci in the Nose in Relation to Antibiotic Treatment*

Carrier State in First Week	No.	Patients Acquiring Penicillin-resistant Strains in Ward		Patients Not Acquiring Penicillin-resistant Strain	
		Total	No. Given Antibiotic	Total	No. Given Antibiotic
No *Staph. aureus*	250	77	52 (42)*	173	63
Penicillin-sensitive *Staph. aureus*	103	21	12 (12)	82	38
Total	353	98	64 (54)	255	101

* In parentheses, number given antibiotic before acquisition of the resistant staphylococcus.

penicillin-resistant staphylococcus in their nose, in 54 cases after having had antibiotic treatment. Altogether 165 patients had antibiotic treatment, and 64 of them acquired a resistant strain.

The number of patients carrying tetracycline-resistant staphylococci in any one ward was rather small; to study them we have therefore used the material from wards A, B, and C. Altogether 39 patients acquired tetracycline-resistant staphylococci in their noses, but only 7 of them had had tetracycline treatment; 11 other patients were treated with tetracycline but were not observed to become nasal carriers of resistant strains. Of 14 patients who carried a sensitive strain when first swabbed and later acquired a tetracycline-resistant staphylococcus all but two also showed a clear change in phage-type. In one there was a change of doubtful significance, and in a second there was no change in type but other carriers of resistant strains of the type were present in the ward at the time.

Sepsis

Altogether we had records of 1,358 patients, 722 of whom had surgical operations. Seventy-six (5.6%) of the patients developed some infective lesion due to staphylococci during their stay in hospital; 60 (4.4%) had some lesion other than wound sepsis; and 34 (4.7%) of those having operations developed post-operative wound sepsis. Eighteen patients had both wound sepsis and some other staphylococcal lesion.

Post-operative Wound Sepsis

The incidence of staphylococcal wound sepsis was lower in patients who never yielded staphylococci from the nose during their stay in hospital than it was in patients who were found to be carriers (Table IV). Of the 342 patients who were not nasal carriers at any examination, only 7 (2%) developed staphylococcal wound sepsis, as compared with 27 (7.1%) of the 380 patients who were carriers.

There were 104 patients who were not carrying *Staph. aureus* when swabbed during the first week after their admission to the ward but who became carriers later. Their incidence of post-operative sepsis (6.7%) was very similar to that of the 276 patients who were carriers in the first week. Of the 276 patients who carried *Staph. aureus* at their first swabbing, 89 showed a change of phage-type of their nasal staphylococcus while in the ward; 6 of the 89 (6.7%) developed wound sepsis, in 4 cases with a staphylococcus of the same type as that acquired in the ward.

Altogether 18 of the 27 nasal carriers who developed post-operative sepsis yielded a staphylococcus from their wound of the type they harboured in their nose.

TABLE IV.—*Wound Sepsis in Relation to Nasal Carrier State*

Nasal Carriage of *Staph. aureus*	No. of Patients having Surgical Operations	Developing Wound Sepsis Due to Staphylococci					
		Of Type Present in Nose		Different in Type from those in Nose		Total	
		No.	%	No.	%	No.	%
a: Never	342	—		7	2·0	7	2·0
b: Not carrier at first swabbing; acquired *Staph. aureus* later	104	7	6·7	0		7	6·7
c: Carrier at first swabbing	276	7	2·5	9	3·3	20	7·3
d: Carrier at first swabbing; acquired new type in ward	89	4	4·5				
e: Total, carriers at some time	380	18	4·7	9	2·4	27	7·1
f: Grand total	722	18	2·5	16	2·3	34	4·7

Note.—The cases of sepsis entered in rows *c* and *d* are respectively those due to staphylococci of the type found at first swabbing and those acquired in the ward.

In only three cases was the nasal staphylococcus not isolated until after the development of wound sepsis; in one case it was first isolated from nose and lesion on the same day. It is worth noting that of the 18 patients, 11 (61%) had become nasal carriers of the relevant staphylococcus during their stay in the ward.

The incidence of infection due to staphylococci different from those carried in the nose is presumably a measure of cross-infection direct to the wound, and one might expect that this would be independent of the nasal carrier state. In fact, 7 (2%) of 342 wounds in non-carriers developed sepsis, and 9 (2.4%) of 380 wounds in carriers developed sepsis due to staphylococci of a different type from that carried in the nose (Table IV).

It was of interest to seek evidence of differences in the "virulence" of the staphylococci in the noses and wounds of these patients. We can do this if we assume that, when the same staphylococcus was isolated from nose and wound, the wound was infected from the nose, and, further, that the nasal carriers were, on average, all equally at risk of acquiring wound sepsis

TABLE V.—*Wound Sepsis in Relation to Nasal Carriage of Drug-resistant or "Virulent" Staphylococci*

	No. of Patients having Surgical Operations	Percentage Developing Wound Sepsis with Staphylococci			
		Same Type as Nose	Different from Nose		Total
			Not Res. or VT	Res. or VT	
	1	2	3	4	5
a: Never carriers	342	—	—	—	2·0*
Some-time carriers:					
b: Penicillin-sensitive strains only	172	4·1	2·9	1·2	8·2
c: Penicillin-resistant strains	206†	5·3	—	1·0	6·3
d: Tetracycline-sensitive strains only	334	3·3	2·4	0·3	6·0
e: Tetracycline-resistant strains	46	15·2	0	0	15·2
f: Non-"virulent" types only	354	2·5	0·3	2·3	5·1
g: "Virulent" types	26	34·6	0	0	34·6

Note.—In columns 3 and 4 "Res." refers to penicillin-resistance in rows *b* and *c* and to tetracycline-resistance in rows *d* and *e*; VT = virulent types, referring to rows *f* and *g*.

* For 7 patients, never carriers, with wound sepsis, the wound staphylococci were penicillin-resistant in 4 cases, tetracycline-resistant in 3, and "virulent" types in 2.

† 1 patient carrying 2 strains—one resistant and one sensitive to penicillin—omitted.

from the staphylococci carried in their nose. As a first step we may compare the experience of patients who were nasal carriers at their first swabbing (and probably in most cases on admission to the ward) with those who became carriers subsequently. There was no more than a slight suggestion that the strains appearing in the nose during the patient's stay in the ward were in general more likely to produce sepsis than those carried at the first swabbing: the "self-infection" rates were 6.7% and 4.5% for the former and 2.5% for the latter group (Table IV, rows *b*, *c*, and *d*).

We next took penicillin-resistance as an indicator of the "hospital" staphylococci (Table V). There was again no more than a very slight suggestion that these strains may have been more virulent than the penicillin-sensitive strains: 5.3% of the 206 nasal carriers of penicillin-resistant staphylococci had wound sepsis due to the type found in their nose, compared with 4.1% of the carriers of sensitive strains.

When the same analysis was carried out for carriers of tetracycline-resistant staphylococci a substantial difference was observed: 7 (15.2%) of the 46 patients who, at any time, had tetracycline-resistant strains in their nose developed wound sepsis with the nasal strain, as compared with 11 (3.3%) of the 334 patients who carried only sensitive strains in their nose.

In a previous paper (Shooter *et al.*, 1958) we suggested that some phage-types of staphylococci were particularly "virulent" and liable both to spread through the ward and to produce septic lesions. During the period of the present survey there were 10 phage-types that produced two or more septic lesions within a short period. These were: 47/53/75/77+; 75/77+; 75/77; 80; 6/42E/47/75v.w.; 187; *52/52A/80*; 3C/71+; *79*; 52/80. We have provisionally taken these as our local "virulent types" and analysed the comparative experience of patients who did or did not become nasal carriers of one or other of these types (Table V, rows *f* and *g*). Of 26 patients who at one time or another carried one of the "virulent" types in their nose, 9 (34.6%) developed post-operative wound sepsis due to a strain of the type carried in the nose.

On the other hand, only 9 (2.5%) of the 354 patients who carried other types developed wound sepsis with their nasal staphylococcus.

The virulent types were responsible for 2 of the 7 cross-infections in non-carriers and 2 of the 9 in carriers. The similarity of these proportions suggests that the colonization of the nose may have been important in conducing to the virulence. It could, however, merely be that nasal carriage offered an opportunity for the staphylococci to get into the wound, either directly or from the skin, in the operating theatre. But in fact only 2 of all 27 cases of wound sepsis gave an indication of arising from theatre infection, and in neither case was the staphylococcus one of the virulent types.

Other Septic Lesions

Table VI and VII also present a similar analysis of septic lesions other than post-operative wound sepsis in relation to nasal carrier state. Not only the trends but the actual rates of infection are remarkably similar to those for wound sepsis. Altogether 4.5% of the 1,319 patients had some septic lesion. The rate in carriers was 6.9% and in non-carriers 2.1%. Twenty-eight (62%) of the 47 infections in carriers were due to staphylococci of the type present in the nose. The incidence of direct cross-infection estimated in the same way as for the wounds was 2.1% in the non-carriers and 2.8% in the nasal carriers. The 37 carriers of virulent types had a 35.1% incidence of apparent self-infection, compared with 2.3% in the 650 other carriers.

The "other septic lesions" included 12 cases in which the patient was admitted with the septic lesion; 4 of these patients carried the same type of staphylococcus in nose and lesion on admission. Altogether 6 of the patients developed their nasal carriage after the appearance of sepsis.

TABLE VI.—*Sepsis Elsewhere Than in Wound in Relation to Nasal Carrier State*

Nasal Carriage of *Staph. aureus*	No. of Patients	Developing Sepsis: Of Type Present in Nose No.	Of Type Present in Nose %	Different in Type from those in Nose No.	Different in Type from those in Nose %	Total No.	Total %
a: Never	632	—		13	2·1	13	2·1
b: Not carrier at first swabbing acquired *Staph. aureus* later	172	11	6·4	8	4·6	19	11·0
c: Carrier at first swabbing	515	16	10·5	11	2·1	28	5·5
d: Carrier at first swabbing acquired new type in ward	111	1	0·9				
e: Total, carriers at some time	687	28	4·1	19	2·8	47	6·9
f: Grand total	1,319*	28	2·1	32	2·4	60	4·5

Note.—The cases of sepsis entered in rows *c* and *d* are respectively those due to staphylococci of the type found at first swabbing and those acquired in the ward.

* An additional 39 patients, none developing sepsis, had no nasal swabs taken.

TABLE VII.—*Sepsis Elsewhere Than in Wound in Relation to Nasal Carriage of Drug-resistant or "Virulent" Staphylococci*

	No. of Patients	Percentage Developing Sepsis with Staphylococci: Same Type as Nose	Different from Nose: Not Res. or VT	Different from Nose: Res. or VT	Total
	1	2	3	4	5
a: Never carriers	632	—	—	—	2·1*
Some time carriers:					
b: Penicillin-sensitive strains only	330	0·6	1·2	1·2	3·0
c: Penicillin-resistant strains	351†	7·4	1·4	1·7	10·0
d: Tetracycline-sensitive strains only	615	2·9	1·6	0·8	5·3
e: Tetracycline-resistant strains	66†	16·7	0	6·1	21·2
f: Non-"virulent" types only	650	2·3	1·5	1·2	5·1
g: "Virulent" types	37	35·1	0	2·7	37·8

Note.—In columns 3 and 4 "res." refers to penicillin-resistance in rows *b* and *c* and to tetracycline-resistance in rows *d* and *e*; VT=virulent types, referring to rows *f* and *g*.

* For 13 patients, never carriers, with sepsis, the staphylococci were penicillin-resistant in 6 cases, tetracycline-resistant in 3, and virulent types in 2.

† For 6 patients, none developing sepsis, the sensitivity of the nasal staphylococci was not known.

Discussion

In considering the aetiology of post-operative sepsis and other hospital infections, the bacteriologist is apt to think in bacteriological terms and to seek to explain the incidence of infection by reference to the sources from which the patient could have become infected. The clinician, on the other hand, is inclined to think of clinical reasons why some patients become septic and others not.

A true understanding of the aetiology of septic complications in hospital patients can be achieved only by a combination of bacteriological and clinical analysis. But we may be reasonably certain that the sepsis would not develop if there were no pathogenic bacteria available, and it is therefore worth plotting the potential sources of infection in the ward. This paper is thus, quite frankly, a bacteriological contribution in which we have tried to show how much of the infection in the patients could have been derived from their own noses, and to what extent this nasal carriage was acquired in the ward.

The figures that we present for the acquisition of hospital staphylococci in the nose of hospital patients serve as a reminder of facts already known. They also offer some confirmation to the observation of Knight, White, and Martin (1958) on the importance of systemic antibiotic treatment in fostering the acquisition of resistant staphylococci in the nose. From the figures of Table III it can be seen that some 64 of the 165 patients given antibiotic treatment acquired penicillin-resistant staphylococci in their nose compared with only 34 of the remaining 188 who were given no such treatment.

It is, however, rather the importance of the acquisition of hospital staphylococci to the individual that we wish to stress. The patients who were or became nasal carriers of staphylococci had three times as much staphylococcal sepsis as those who were never carriers. And, altogether, 18 of the 27 patients with wound sepsis and 27 of 58 patients with other septic lesions (not all different individuals from those with wound sepsis) harboured the same phage-type of staphylococcus in their septic lesion and their nose. Since we found nearly 40 different types of staphylococci in septic lesions, and probably upwards of 200 different types in noses, this frequency of concurrence is clearly enormously greater than would be expected by chance. It appears, therefore, that self-infection is important in the aetiology of the septic lesions.

It is, however, possible either that the lesion infects the nose or that both are infected separately from some other source. The first is unlikely, because in only very few patients were the staphylococci not found in the nose until after the development of sepsis, though, with the relatively long intervals necessarily elapsing between swabbings, exact timing is impossible. The second is possible because there was almost always some other patient infected with the same type elsewhere in the ward, though there were rarely many. In only 4 of the 10 incidents of cross-infection was the spreading type found in any large numbers in the air. But to explain the differing experience of nasal carriers and non-carriers one would have to postulate some general staphylococcal "diathesis" which made those who became nasal carriers also more likely to become infected in their wound or elsewhere. In this case one would hardly expect the nose and lesion to show the same type of staphylococcus with such frequency.

It seems more reasonable to regard the nose as being often the source of the sepsis. The incidence of sepsis due to staphylococci not carried in the nose is then reasonably regarded as an index of the amount of cross-infection conveyed direct to the wound or other site. Cross-infection of this sort was hardly more common in carriers than in non-carriers—a fact that seems to argue against any general proneness in the carriers.

The analysis also offers some further support for the idea that some staphylococci are more virulent than others. We did not suffer any extensive outbreaks of cross-infection, but, though nearly 40 different types produced sepsis, only 10 types were responsible for two or more cases of sepsis—that is, produced evident cross-infection—and these did so at widely scattered times. Over 30% of the patients who became nasal carriers of one or other of these strains also developed some septic lesion, compared with 5% of those carrying other strains.

The use of phage-type as a guide to virulence has the disadvantage that it takes time to get the typing done, and that there are clearly a great number of types that can sometimes produce epidemics (see Williams, 1959). For several years tetracycline-resistance has been used in some wards at St. Bartholomew's Hospital as a presumptive guide to virulence. In the present study only 6 of the 10 virulent types were tetracycline-resistant, but it needs to be remembered that we took the production of only two cases of sepsis as an indication of "virulence." Because of this, and because not all tetracycline-resistant strains were virulent, the incidence of sepsis in the carriers of tetracycline-resistant strains (15%) was not so high as in carriers of the locally "virulent" types. Nevertheless the excess of this rate over that for all carriers is a clear vindication of the policy of regarding the tetracycline-resistant strains as potentially dangerous.

The tentative picture that seems to emerge from this survey is this: in about half the cases of sepsis the staphylococci in the lesion could have been derived from the patient's own nose, and in half of these possible self-infections the nasal strain had certainly been acquired in the ward. The latter proportion is probably really greater than this because a rather large number of patients were not swabbed until after they had been in the ward several days. About 40% of the cases of sepsis, both in wounds and elsewhere, were due to a small number of apparently more virulent types of staphylococci, and almost all the patients infected with these types had them in their nose as well as in their lesion.

These results suggest that the role of the nose as a source of self-infection is not confined to the relatively trivial septic lesions studied in the past, a conclusion amply confirmed by Weinstein (1959) in an analysis of sepsis in 125 patients undergoing thoracic surgery. The results also suggest that the incidence of sepsis ought to be reduced by the elimination or prevention of the nasal carriage of staphylococci. This might be achieved by measures designed to protect susceptible patients from exposure to those already infected (whether they have septic lesions or are symptomless carriers) or by topical application of antibiotics to the nose. Gillespie (1958) has already reported favourably on the latter method, though Weinstein (1959), in a very different situation, seemed to have no success.

Summary

Of 602 patients swabbed within a few days of admission to a male surgical ward, 38% carried *Staphylococcus aureus* in their nose, and 13% carried penicillin-resistant strains. Of 25 swabbed after eight weeks in the ward 68% were carriers and 52% had resistant strains.

Patients who were non-carriers on admission acquired resistant strains in the ward more readily than those initially carrying sensitive strains. 64 of 165 patients treated with antibiotics acquired penicillin-resistant strains in their noses; 39 patients acquired tetracycline-resistant strains in their noses.

The incidence of post-operative staphylococcal wound sepsis was 2% in 342 patients who were never nasal carriers of staphylococci and 7.1% in the 380 who carried at some time. In about half the cases the sepsis was due to a staphylococcus of the same type as was found in the nose. Of patients who were nasal carriers of one or other of 10 apparently more virulent types, 35% had wound sepsis, in all cases due to the nasal type of staphylococcus.

Of a total of 1,319 patients 4.5% developed sepsis elsewhere than in a wound. The relation to nasal carriage was very similar to that of wound sepsis.

The results suggest that the incidence of sepsis might be reduced if acquisition of staphylococci in the nose could be prevented.

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References

Anderson, E. S., and Williams, R. E. O. (1956). *J. clin. Path.*, **9**, 94.
Gillespie, W. A. (1958). *Med. J. S.-W.*, **73**, 56.
Knight, V., White, A. C., and Martin, Margaret P. (1958). *Ann. intern. Med.*, **49**, 536.
Roodyn, L. (1954). *Brit. med. J.*, **2**, 1322.
Shooter, R. A., Smith, M. A., Griffiths, J. D., Brown, Mary E. A., Williams, R. E. O., Rippon, Joan E., and Jevons, M. Patricia (1958). Ibid., **1**, 607.
Valentine, F. C. O., and Hall-Smith, S. P. (1952). *Lancet*, **2**, 351.
Weinstein, H. J. (1959). *New Engl. J. Med.*, **260**, 1303.
Williams, R. E. O. (1958). *Publ. Hlth Rep. (Wash.)*, **73**, 961.
—— (1959). *Lancet*, **1**, 190.
—— and Miles, A. A. (assisted by Barbara Clayton-Cooper and Brenda Moss) (1949). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 266.

SOME COMMON COMPLICATIONS AFTER PROSTATECTOMY

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The scope of prostatectomy has steadily increased year by year, resulting in many bad-risk patients being subjected to operation. Methods specially needed in these cases have already been described (Cosbie Ross, 1936), There has always been a proportion of cases with post-operative complications, but the increasing average age of the patient and the number with intercurrent medical conditions have made it necessary to take special precautions to deal with them.

We thought, therefore, that it would be of interest to investigate and record the complications in 100 cases of prostatectomy. These patients were not selected in any way. Wilson Hey prostatectomy was carried out in 65 cases, retropubic prostatectomy in 3, and cold-punch resection (perurethral) in 32.

It is our custom to perform retropubic, Wilson Hey, and perurethral prostatectomy according to the size of the prostate and other indications (Cosbie Ross, 1954). As it happens, in this series the Wilson Hey method preponderates over the retropubic, but this is coincidental, and the corresponding figures for the year 1952 were: retropubic, 16; Wilson Hey, 12; cold punch, 25; suprapubic with drainage, 9. A similar pattern emerged in other years when the number of transvesical and retropubic operations was more approximate.

The point we wish to emphasize is that the type of operation apparently makes no essential difference to the incidence of complications which may follow in the train of any of the modern procedures.

With modern methods of anaesthesia the danger period of prostatectomy has shifted from the actual operation to the first few post-operative weeks, and it is to some of the difficulties arising during this stage that we wish to draw attention.

It is not intended to deal with immediate or reactionary haemorrhage, as at the present time bleeding does not constitute the serious menace of the past. The modern operations, including perurethral resection, appear to cope fairly successfully with haemorrhage. None of the patients developed osteitis pubis. The post-prostatectomy flap or valve is rarely encountered now that operation is carried out under direct vision and trigonectomy performed.

Table I shows the preponderance of the aged in the series. The main complications were: incontinence (temporary), post-meatal stricture, persistent pyuria, epididymitis, and a temporary suprapubic leak.

TABLE I.—*Age Distribution*

Age in years	50–55	56–60	61–65	66–70	71–75	76–80	81–85	86–90
No. of cases	5	8	18	21	22	19	5	2

Temporary Incontinence

Temporary incontinence is rarely mentioned in the literature, but it causes much distress and anxiety to the patient if it has not been explained to him that it is transient. There was no case of permanent incontinence in this series.

We have been convinced for some time that the incidence of this complication increases with age and that those over 80 are especially prone to the condition. Post-operative incontinence is almost invariably temporary, but in one of our patients it persisted for three to four months before recovery of satisfactory control. It is not generally recognized that continence is a relative quality and that the intravesical pressure increases as the patient rises from the recumbent position to sit up in bed (Tinckler, 1955). A further increase of pressure can be recorded as the patient stands upright, and a final increase on abdominal straining, coughing, etc. Stress incontinence may therefore be classified into four stages or degrees: stage 1, incontinence only on coughing or straining; stage 2, incontinence on assuming upright posture; stage 3, incontinence on sitting up in bed; and stage 4, incontinence when recumbent.

The type of operation performed appeared to have little influence on the incidence of incontinence, which occurred in roughly the same proportion in each type, although possibly less often in punch prostatectomy.

A simple method of sphincterometry has been used in all our patients exhibiting any degree of incontinence a week after removal of the catheter.

Technique of Sphincterometry

Sphincterometry is a technique for measuring the resistance of the urethral passage. Although the term suggests a measurement of the sphincter mechanism only, it is in fact a function of the total resistance to the movement of fluid along the urethra, probably conditioned more by sphincter action than by any other factor. There are, of course, other factors, such as the elasticity of the structures around the prostatic urethra. It has been shown that complete incontinence does not necessarily follow a pudendal-nerve block (Caine and Edwards, 1958) or division of the external sphincter (Cosbie Ross, Gibbon, and Damanski, 1958).

The armamentarium required is as follows: (1) A St. Peter's type urethral catheter, size 10F. (2) A Cunningham penile clip. (3) A manometer, constructed by affixing a glass tube to a piece of wood on which a scale is calibrated in centimetres. (4) An infusion flask containing sterile saline, preferably dyed with a little methylene blue to enable the fluid level to be more easily seen. (5) A glass Y-connexion and rubber tubing, incorporating a drip chamber connecting the infusion flask, manometer, and urethral catheter to the Y-piece.

It is a convenience to have the rubber tubing, glass connexion, and urethral catheter (together with a couple of towels and some gauze swabs) wrapped up in a large towel and autoclaved so as to be ready for use as required.

The patient empties his bladder immediately before carrying out the test. As some hospital beds sag in the middle it is useful to raise the patient's pelvis by placing a pillow underneath his buttocks. A drip stand is fastened to the foot of the bed and the manometer hung therefrom, the height of the manometer being adjusted

so that the zero mark is level with the patient's symphysis pubis. With aseptic precautions the catheter is inserted into the anterior urethra until the resistance of the external sphincter is felt, and then withdrawn slightly. To prevent reflux around the catheter a Cunningham penile clip is applied to hold it snugly in the urethra. Finally, the tubing is connected up, ensuring that bubbles of air are displaced by thoroughly flushing the system with sterile water.

The object of the test is to determine the minimum hydrostatic pressure at which fluid will flow *freely* through the urethra into the bladder, and the reading is taken to be an index of the total resistance of the passage. It is ascertained by elevating the infusion flask and allowing saline to run into the bladder.

To begin with, the reservoir is held just above the level of the symphysis, then slowly raised, and the behaviour of the fluid passing through the drip chamber is observed. At first there is a steady drip until a level is reached at which fluid suddenly starts to flow in an unbroken stream. This indicates that all resistance has been overcome by the hydrostatic pressure, which is recorded as the height of the column of fluid in the manometer. By carrying out this procedure under *x*-ray screening, using 12% sodium iodide, the opening-up of the posterior urethra can be seen when the flow changes from a drip-rate to a steady stream.

Results obtained from this test on normal and on incontinent subjects are summarized in Fig. 1. Not unexpectedly the latter show less sphincteric tone than

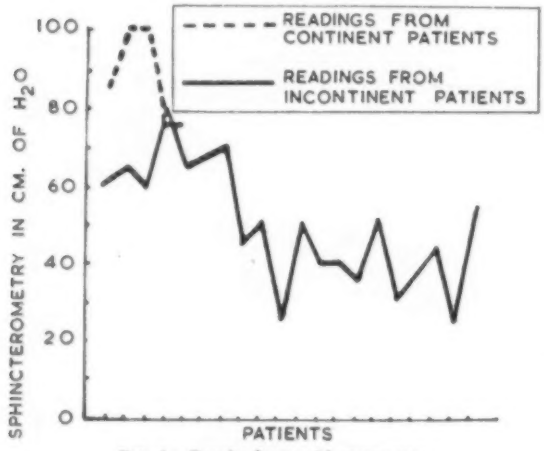

FIG. 1.—Results from sphincterometry.

the former, although readings are somewhat variable. The minimal level of sphincter resistance which will ensure continence is approximately 80 cm. of water.

We have attempted to classify our patients with any degree of post-operative incontinence in the various age groups (Fig. 2); it was found that the older the patient the longer the incontinence appeared to linger (Table II).

TABLE II.—*Duration of Incontinence and Age of Patient*

Incontinence in Post-operative Days	Age of Individual Patients	Average Age
0–7	65, 73, 73, 57, 72, 76	69
8–14	70, 77, 74, 85, 59	73
15–21	78, 87, 70, 77, 79, 74, 80, 83	78
21+	84, 73, 69, 88, 72	78

All in all, incontinence is a troublesome complication which, in all probability, clears up in the course of weeks.

We have found perineal faradism and ephedrine helpful and sometimes use a Cunningham clip. In old and feeble patients it has been necessary to use Paul's tubing fixed to the penis with sleek strapping for the

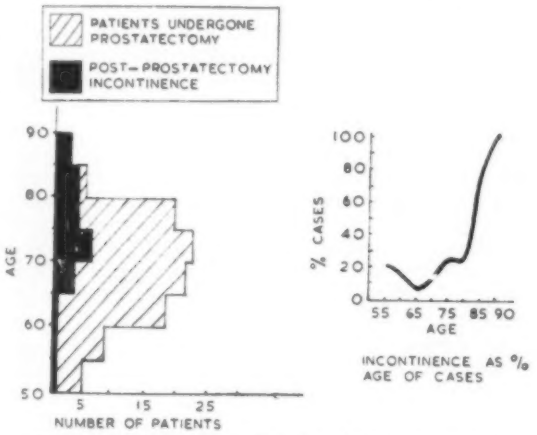

FIG. 2.—Incontinence as a proportion of cases by age group.

first few days after removal of the catheter, and we can recommend the efficacy of this simple and easily applied device.

Post-meatal Stricture

Johnston (1953) pointed out that a stricture in this situation, approximately ½ in. (1.3 cm.) from the external urinary meatus, was by no means rare, and occurred in 20% of patients irrespective of the type of prostatectomy. In the series of patients investigated by Johnston a red rubber Harris catheter was used during the post-operative period, whereas in the present series a latex two-way catheter was inserted in almost every instance. There was a marked drop of incidence of this complication, and it seems reasonable to attribute the improvement to the latex catheter, as otherwise the operative and post-operative conditions were identical. In the 100 patients under review post-meatal strictures were found in only two. It would seem that this particular complication has been largely eliminated by avoiding the use of red rubber catheters. Other factors, such as the size of the resectoscope or the catheter, the duration of post-operative catheterization, and the lumen of the urethra, although important, do not seem as crucial as the actual constitution of the catheter itself. At the same time it is important to exclude such a development, as the condition appears to respond well to early dilatation and may not tend to recur. It is our practice to pass a No. 20F catheter 10 days after operation, not only to collect a sterile specimen of urine for culture and sensitivity studies but also to exclude a stricture.

Persistent Pyuria

Pyuria constitutes one of the most perplexing and formidable complications after prostatectomy and also implies a criticism of present methods, as the number of patients with infected urine rises sharply during the immediate post-operative period (Miller *et al.*, 1958). In the present series 33 had urinary infection before prostatectomy. During the first four weeks after

operation no fewer than 83 were found to be infected in spite of the fact that it is our practice to set up the closed-drainage system in the theatre before the patient returns to the ward. Additional precautions include the enclosure of the penis and extremity of the catheter in a sterile chamber formed by a roll of "cellophane" secured above and below by sleek strapping. The catheter is usually removed on the fourth post-operative day.

The routine administration of antibiotics immediately after the operation does not seem to influence the tendency to infection. In the earlier period of our investigation it was customary to give 500,000 units of penicillin twice a day and 1 g. of streptomycin once a day by the intramuscular route. The discontinuance of this regime was not followed by any perceptible increase of infection. We discarded this procedure partly because of the reports of patients developing fatal colitis under such a regime (Webster, 1958), and partly from the experience of colleagues, who appeared unanimous in considering that the umbrella method was of little value (M. Boyd, 1957, personal communication). It is difficult to explain this frequent development of post-operative infection. It has, however, been shown that in the paraplegic bladder it is difficult to render the urine sterile by means of antibiotics for more than a brief period if there is any dilatation of the ureter or hydronephrosis (Cosbie Ross, Gibbon, and Damanski, 1957). All of our patients had a pre-operative intravenous pyelogram, and many showed evidence of hydronephrosis and hydroureter. We have therefore attempted to correlate the incidence of post-operative infection with back-pressure on the upper urinary tract. This is shown in Table III. The figures suggest that

TABLE III.—*Pre-operative I.V.P. Findings and Persistent Pyuria*

Pre-operative I.V.P.	No.	No. with Sterile Urine within 6 Months
Normal	68	14 (20%)
Showing definite dilatation of urinary tract	25	3 (12%)

if the patient had a normal intravenous pyelogram before operation he is twice as likely to achieve a sterile urine six months after prostatectomy as a patient with pre-operative evidence of back-pressure on the upper urinary tract. It is obvious that this is not the only factor, but it might well be of considerable importance.

A brief study of the bacteriology was not without interest, and the following points seemed to us the most important: (1) Infection reached its peak within four weeks of the operation and then progressively diminished with each month. At the end of six months 50% of patients had sterile urine (Fig. 3). (2) *Escherichia coli* and *Proteus vulgaris* (in this order) preponderated both before and after operation. Other organisms were found less frequently, and appeared to be of much less importance (see Table IV). It should be noted that proteus infection appears to rise sharply after prostatectomy.

FIG. 3.—Prostatectomy and urinary sepsis.

TABLE IV.—*Urinary Infection*

Pre-operative urine	33 infected cases
E. coli	16
Proteus	7
Bact. aerogenes	4
P. pyocyanea	4
Staph. pyogenes	2
Post-operative 0–4 weeks	83 cases
E. coli	40
Proteus	36
Bact. aerogenes	3
Ps. pyocyanea	3
Staph. pyogenes	—
No pus or organism	1 (1·2%)
Post-operative 6–12 months	20 cases
E. coli	6
Proteus	—
Bact. aerogenes	3
Ps. pyocyanea	—
Staph. pyogenes	1
No pus or organism	10 (50%)

These figures of post-operative infection follow closely the experience of other writers, notably Caine (1953), who found that the majority of the patients after prostatectomy showed evidence of infection, the infection generally clearing up within two to four months of the operation. The surprising feature is that the post-operative infection does not seem to have diminished in spite of the fact that various factors to which it has been attributed have largely been eliminated in the present series. For example: (1) So far as possible, the passage of a catheter before operation has been avoided. (2) Preliminary suprapubic drainage was carried out on only 11 occasions, this being necessary owing to coronary thrombosis, hemiplegia, and other serious acute medical conditions. (3) The routine preliminary intravenous pyelogram and the cystoscopy carried out immediately before operation have made it unlikely that a diverticulum has been overlooked. It has been our practice to remove a large diverticulum when performing the prostatectomy. (4) It has been suggested that the lower end of the ureter might be damaged in performing the trigonectomy. In order to avoid this possibility we have located the ureteric orifices with a probe as a routine measure before resecting the "posterior wedge." (5) A catheter is passed on the tenth post-operative day in order to exclude stricture formation.

Our view is that, in addition to the back-pressure on the upper urinary tract, post-operative infection is often due to the fact that there is inevitably a large granulation-lined cavity, which requires several weeks to epithelize. It is during these first four weeks, while epithelization is taking place, that infection reaches its peak.

Epididymitis

Vasostomy waxes and wanes in popularity, but it is an undoubted fact that the incidence of epididymitis is greatly reduced by the small operation. Caine (1954) reports an incidence of 25% when the vasostomy is omitted, compared with 7% when the operation is performed. It has been our practice to carry out vasostomy in all cases except in punch prostatectomy, the incidence in the present series being 7%. We do

not consider that vasostomy can be dispensed with until such time as post-operative infection has been eliminated. Incidentally, we agree with Caine's view that the administration of antibiotics after operation has no prophylactic value whatsoever. (Epididymitis occurred in equal numbers in the antibiotic and non-antibiotic group.)

We have also attempted to evaluate two methods of performing vasostomy: division and ligation *vis-à-vis* the application of diathermy forceps to the vas. The diathermy method was used as a routine on the left vas, whereas the right was divided and ligated. It was concluded that there was little to choose between the two procedures, but that, on balance, the division and ligation method appeared to be the more satisfactory.

Temporary Suprapubic Leak

In the present series there was no case of incisional hernia, a fact we attribute to the routine use of a transverse suprapubic incision. In fact, since adopting this incision several years ago only one incisional hernia has been seen, and we do not think that it is justifiable to perform prostatectomy through a vertical midline incision in aged and debilitated patients. On the other hand, in 27% a suprapubic leak developed. The leak was of a temporary character and healed after a few days' catheter drainage. Only in one patient was it found necessary to excise and resuture the wound. Urinary leaks occurred especially in aged and feeble patients who had concomitant medical diseases, such as coronary or cerebral thrombosis, or who presented with the troublesome combination of chronic uraemia and secondary anaemia.

In an attempt to prevent this complication it is our practice to suture the bladder wall with three rows of continuous suture in the Wilson Hey operation, and to suture the prostatic capsule with two rows of sutures in the retropubic operation, using an eyeless needle on No. 1 twenty-day catgut.

Conclusions

The increasing number of aged and feeble patients submitted to prostatectomy inevitably produces a group of post-operative complications which require special investigations and special treatment.

In an attempt to evaluate these complications a study has been carried out in a series of 100 patients subjected to prostatectomy.

A temporary incontinence was noted in approximately a quarter of the present series. A simple method of "sphincterometry" was used in the assessment of this incontinence.

Post-meatal stricture appears to have been largely eliminated by discarding the red rubber catheter. With the use of a latex catheter only 2% developed a urethral stricture.

Post-operative infection continues to be the most obstinate problem, *E. coli* and *Pr. vulgaris* preponderating. It is suggested that back-pressure and hydronephrosis before operation are factors in encouraging infection. It is also pointed out that the peak period of infection occurs during the first four weeks, during which the prostatic cavity is in the process of epithelizing.

The incidence of epididymitis with vasostomy was 7% in this series.

A temporary suprapubic leak occurs in a proportion of patients, and is probably due to a lack of healing ability in elderly and debilitated patients.

References

Caine, M. (1953). *Brit. J. Urol.*, **25**, 9.
—— (1954). Ibid., **26**, 205.
—— and Edwards, D. (1958). Ibid., **30**, 41.
Johnston, J. H. (1953). Ibid., **25**, 155.
Miller, A., Gillespie, W. A., Linton, K. B., Slade, N., and Mitchell, J. P., (1958). *Lancet*, **2**, 608.
Ross, J. C. (1936). *Brit. med. J.*, **2**, 1297.
—— (1954). Ibid., **2**, 1201.
—— Gibbon, N. O. K., and Damanski, M. (1957). *Lancet*, **2**, 520.
—— —— —— (1958). *Brit. J. Urol.*, **30**, 204.
Tinckler, L. F. (1955). Ch.M. Thesis. Liverpool.
Webster, C. U. (1958). *Lancet*, **2**, 1036.

TOILET TRAINING AND ENURESIS

BY

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It has often been claimed that a major factor in the production of enuresis is the method of toilet training. Some workers—for example, Anderson (1930), Stockwell and Smith (1940), and Bakwin (1949)—found that most enuretics had received insufficient training, but others followed Huschka (1943), who incriminated coercive methods, including early training. Bostock and Shackleton (1951, 1952) supported Huschka at first, but in 1956 they claimed that early training alone was fundamental when they discovered that some enuretics had received gentle training.

Controls using normal children had been rarely studied in sufficient numbers to establish a pattern with which enuretics could be compared. In the U.S.A., for example, Despert (1944) could compare 60 normal children with 14 bedwetters, but found early training rare in both groups. In two larger series, Davis and Havighurst (1946) found that bowel training began in the lower classes below the age of 6 months in 23% of cases, and Klatskin (1952) reported that it began under the age of 1 year in 66%. The largest survey in this country revealed a marked difference. Douglas and Blomfield (1958) found that 60% of 3,990 children, in all social groups, born in 1946 began to be "potted" within the first two weeks of life but that enuresis occurred more often with those who began later.

Sufficient conflict of opinion exists both as regards the ages at which toilet training begins and as regards its relationship to enuresis to justify reassessment and at the same time to present additional data. It was felt to be particularly misleading to study the enuretic outside the context of the family unit with respect to toilet training, since a comparison with the dry siblings was thought essential.

Method and Scope of Investigation

Children were defined as enuretic who were still wet at night at the age of 4 years in the absence of any discoverable organic cause.

Their mothers were closely questioned personally regarding the age at which toilet training was begun, whether it was carried out strictly or not, whether it was resisted or resented, and the ages at which bladder and bowel control were achieved, if at all. The position of the child in the family was noted, and the same questions

were posed concerning the siblings if over 2 years old, since by that age complete data on control might be expected in most cases. If the answers were vague owing to a poor memory the entire family was excluded. In any event, it was considered unreasonable to expect accuracy regarding children who were 10 or over, and so only families with the eldest child under 10 were accepted. In this manner dry siblings between 2 and 10 years of age acted as controls for the enuretics in their family. Children with encopresis with or without enuresis were thought to constitute a separate if allied problem, and they and their families have therefore been excluded from this survey but will be the subject of a further report.

After these selections had been made there remained for consideration 175 children between the ages of 4 and 10 who had been persistently wet since birth and who came for treatment of this condition to four hospitals and two local-authority clinics in east and south-east London. The great majority belonged to the working or artisan classes. A further 50 enuretics, past or present, were discovered in their families, bringing the total to 225. There were 174 dry siblings to act as controls.

However useful these dry children were for purposes of comparison, they cannot be regarded as representative of the child population at large, if only because the strong family history of enuresis so often present might make mothers anxious to avoid its appearance in their offspring. Therefore a further control series was obtained from consecutive out-patients between the ages of 2 and 10, provided their mothers possessed reliable memories and provided also there was no personal or family history of enuresis or encopresis. It was felt necessary to exclude those families with one or more children who did not become clean—that is, achieve bowel control—until 2½ or dry at night until 3, since the latter would be considered enuretic and the former encopretic by some workers in this field.

After this selection there remained 174 families comprising 202 dry children seen at the out-patients department, together with 182 normal siblings in the same age range (total 384), to act as a contrast group to the "enuretic families." These children are referred to as the "controls," although it must be admitted that the data on these dry children may not accurately reflect current training practice or achievement, for among the children were some with psychosomatic symptoms, abdominal pain, asthma, etc.

Distribution of Enuretics in Families

Among the 165 families with 225 enuretics, there were 142 boys and 83 girls with 83 boys and 91 girls among the dry siblings. Table I shows the family ranking of the wet and the dry children in these "enuretic families." It would appear that the larger the family the higher the proportion of enuretics among the siblings, so that with four siblings or over there were almost two cases per family. (In one family, not included in this survey because of the wide age limits of the seven children, all had been enuretic, five clearing up between 7 and 8, one at 11, and the youngest being still wet at 7 years of age.) With regard to sex differences, whereas in 2-sibling families boy enuretics outnumber girls by 2 to 1, this disparity disappears as families become progressively larger, with a decreasing proportion of boys becoming enuretic. This finding

TABLE I.—*Congenital Enuresis: Family Position of Cases*

Family Size		Total Families	Family Ranking 1st	2nd	3rd	4th	5th	6th	Total Cases
Only children	Wet	28	28						28
2 siblings	Wet	78	44	45					89
	Dry		34	33					67
3 ,,	Wet	35	20	23	16				59
	Dry		15	12	19				46
4 ,,	Wet	12	4	5	6	7			22
	Dry		8	7	6	5			26
5 ,,	Wet	10	4	5	3	5	6		23
	Dry		6	5	7	5	4		27
6 ,,	Wet	2	1	1	1	0	1	0	4
	Dry		1	1	1	2	1	2	8
Total ..		165	165	137	59	24	12	2	399

may be explained to some extent by the larger families to be found among the lowest social classes, in which Douglas and Blomfield found enuresis among girls nearly as common as among boys.

From Table I it may also be deduced that the eldest child is not more likely to be wet than the second-born: this constitutes some evidence against sibling jealousy being an important factor, but in families of three siblings and over there is a slightly greater tendency for the second-born to be enuretic, so that the question of jealousy must remain undecided. It may also be relevant to point out that the inexperience of mothers in handling their first-born children does not appear to make them more liable to bed-wetting.

Time of Beginning Toilet Training

The age at which potting began was readily given as a rule, but even to such a simple question a few mothers referred to the initial attempt, which was quickly abandoned when found to be of "no use." No differentiation between bladder and bowel training could usefully be made. In this survey toilet training refers to a routine even if carried out irregularly, and not to the perfunctory trial which can only be regarded as a brief experiment. Perhaps this difference in interpretation may partly explain the 60% of children potted within the first two weeks of life in the series of Douglas and Blomfield. In any event, training under the age of 9 months (at the earliest) can only refer to "catching" a stool, usually after a feed, or to urine, after a nap, in order to save laundering but more often to "get the baby used to the feel of the potty"—that is, to condition him. It is therefore a tribute to the mother's skill in anticipation.

Although mothers gave the onset of training to the nearest month, in order to make comparisons easier the various ages have been grouped in Table II into three

TABLE II.—*Relationship Between Time of Beginning Training and Family Ranking of Enuretics, Dry Siblings, and Controls*

	Training Periods: Early (<3 Months)	Middle (3–9 Months)	Late (>9 Months)	Total
Enuretics:				
First-born and only	27 (27%)	42 (42%)	31 (31%)	100
Later-born	37 (30%)	47 (38%)	41 (33%)	125
Dry siblings:				
First-born	26 (41%)	26 (41%)	12 (19%)	64
Later-born	26 (24%)	52 (47%)	32 (29%)	110
Controls:				
First-born and only	62 (32%)	83 (43%)	48 (25%)	193
Later-born	53 (28%)	80 (42%)	58 (30%)	191
Total	231 (30%)	330 (42%)	222 (28%)	783

periods only: early (under 3 months), middle (3–9 months), and late (over 9 months). It will be seen that no significant difference exists in all groups of children in the percentage trained in each of the three age periods except for earlier training in first-born dry siblings ($P<0.05$). Later-born children tend towards later training except in the enuretic group in which even the first-born tend slightly towards later training. This trend towards somewhat later training in the enuretic group supports the finding of Douglas and Blomfield and rejects early training as a factor in producing enuresis.

Late training is also unlikely to be a factor because the proportion of enuretics who were trained in the late period is not significantly greater than that noted in the later-born dry siblings and controls. Only five mothers thought the late training of their first-born enuretic children was involved in causing enuresis and therefore changed to a much earlier start with subsequent offspring, but among the controls six mothers did likewise, though for different reasons.

Strictness

Training is here regarded as strict if rigidly performed at given intervals, usually with punishment—for example, slapping, scolding, and arousal of disgust. One mother trained her baby as she did her puppy, by thrusting his excreta in his face, while more than one propped the baby up on the potty with pillows and left him there until something happened, however long it took. Non-strict training is defined as following a more haphazard routine without punishment of any kind, but included in this definition is the lax "training" given by mothers who potted only when they had the time or inclination; this method was prevalent in large families, with twins, and when one baby quickly followed another. Wide latitude was thus left in the interpretation of non-strict training in order to concentrate on those mothers who used coercion as an ancillary aid. Almost certainly some mothers prevaricated for fear of criticism, and therefore the results can only be regarded as approximately true.

When early training is decided upon it is likely to be more strict than with later training in all groups of children, and this tendency is particularly marked among the enuretics who are first-born or only children. For later-born children no difference between enuretic and dry children appears. It is difficult to believe that strictness *per se* can be a factor in producing enuresis solely in the first-born, and then only if training is started early. It is more likely that, expecting trouble from a family history of enuresis, some mothers would train especially their first-born more strictly, but many others seemed to prefer later training combined with laxity.

That increased leniency also has little bearing on the aetiology of enuresis is shown by the finding that if training began after nine months the low incidence of strictness was the same in the first-born enuretics and controls and in the later-born enuretics and dry siblings.

Some mothers of enuretic children openly believed their methods of training were at fault, and decided, after the first-born was enuretic, to change in the direction of greater strictness (14% of mothers did so, against only 3% of the controls), but more thought they had been too strict. Such variations indicative of the perplexity of some mothers of enuretics were rarely seen in the control series, in which the same pattern of training was carried out in all children irrespective of family rank. But, in any case, greater strictness or greater leniency alone does not appear to be responsible for the persistence of bed-wetting.

Resistance

Whether coercion was used or not, many babies resisted their training by the time they were able to walk. They expressed their disapproval by screaming or struggling at the sight of the potty (active resistance), or, in fewer cases, by calmly sitting on it until the mother became tired, releasing their sphincters the moment the potty was removed (passive resistance)—"He did not know what the potty was for." The reaction of some mothers to rebellion was to intensify their efforts and to try to impose their will by force—that is, by strict training—but many others accepted the situation, and, in spite of requestioning, denied they applied any form of punishment.

It is probable that it is this resistance which made some mothers believe that their methods had been ill-conceived, and so, through feelings of guilt, may not have given accurate replies to questions related to the strictness or otherwise of their training. But the impression gained was that they were truthful and frank when it came to answering questions regarding resistance.

The total number of children who resisted actively or passively was 151 out of 783, distributed in Table III

TABLE III.—*Relation Between Strictness of Training and Resistance*

	Training Periods						Total Resisted
	Early		Middle		Late		
	No.	Resisted	No.	Resisted	No.	Resisted	
Enuretics:							
Lenient	35	7 (20%)	59	18 (31%)	59	18 (31%)	28% } 37%
Strict ..	29	12 (41%)	30	19 (63%)	13	9 (69%)	55½% }
Dry sibs:							
Lenient	33	2 (6%)	59	3 (5%)	39	2 (5%)	5% } 9%
Strict ..	19	2 (11%)	19	6 (32%)	5	0	19% }
Controls:							
Lenient	76	11 (14%)	132	15 (11%)	81	9 (11%)	12% } 14%
Strict ..	39	10 (26%)	31	5 (16%)	25	3 (12%)	19% }
Total	231	44 (19%)	330	66 (20%)	222	41 (18%)	19%

according to the declared strictness or leniency of the training. It will be seen that there is a highly significant difference ($P<0.01$) between the resistance put up by enuretics (37%) and that shown by the dry siblings and controls. The percentage for the controls is higher than for the dry siblings, perhaps because among them were children suffering from psychosomatic illness to which methods of toilet training may have been related (Huschka, 1943).

Enuretics resisted even lenient training more than did the other two groups, but were twice as likely to resist if trained strictly. This was also true for the controls, but only if trained early; while with the dry siblings most resistance was demonstrated with training in the middle period. Least resistance was shown by enuretics if trained early, suggesting again that early training is not more conducive to enuresis than later training.

With regard to family ranking, in all three groups the later-born showed a slight trend towards less resistance than the first-born, with the exception of the dry siblings, among whom, in the middle period only, the converse was true.

In general, however, it may be concluded that resistance to training plays a more important part than any of the other factors so far considered.

Sex Differences

It is well known that enuresis is more prevalent among boys than among girls. The only differences detected in this series with regard to toilet training is a slight tendency towards later and more lenient training among girls. This applied to the controls as well as to the enuretics, but the converse was true in the case of the dry siblings. Resistance was shown in all groups equally except in the late training period, in which twice as many boys resisted as girls.

Time of Achievement of Sphincter Control

Table IV shows the effect of resistance to training on bowel and bladder control. It was found that the dry

TABLE IV.—*Relationship Between Time of Beginning Training, Resistance, and Sphincter Control (in Months)*

		Resistance	Training Periods: Early	Middle	Late	Average
Enuretics	Clean ..	No	18	19	23	20
		Yes	23	21	23	22
	Dry by day ..	No	22	25	28	25
		Yes	27	29	29	28
Controls and dry sibs	Clean ..	No	15	15	17	16
		Yes	18	20	22	20
	Dry by day ..	No	17	17	20	18
		Yes	20	22	23	22
	Dry by night	No	19	19	21	20
		Yes	23	25	24	24

siblings and controls were almost identical in their achievement of control, and so in this table they have been grouped together. All children, both dry and wet, show a tendency towards later sphincter control if training is begun late—a finding which confirms that of Douglas and Blomfield.

Table IV also shows that enuretics become clean and dry by day (if at all) later than the controls even if they do not resist training. In addition, both enuretics and controls were later in becoming clean and dry if there was resistance to training irrespective of when training began. These results would have been even more striking if those enuretics who delayed bowel control until the age of 2½ had been included, but, being thought possibly encopretic, they were omitted from this survey.

With regard to family ranking, later-born children of all groups became clean and dry by day and by night (if not enuretic) about a month earlier than the first-born. Girls likewise were earlier to achieve control, becoming clean two months earlier on the average and dry by day one and a half months sooner than boys; if trained early they became dry by night two and a half months sooner, but only one month earlier if trained late. This finding confirms the well-known fact that boys are "harder to train." Despert (1944) has attributed the relative success of girls to the fact that boys have to learn two methods of micturition, sitting and standing, but the greater aggressive tendencies of boys may be a more important factor.

Strictness in training in all groups showed a slight tendency towards earlier control, provided, however, that no resistance was demonstrated.

Discussion

The earliest frustrating experiences of infancy include unsatisfied hunger, napkin-changing, and toilet training. But, whereas infant-feeding is becoming more and more permissive, this is not yet the rule with regard to excretion habits, although in the past decade propaganda directed towards non-strict and later training has been in some measure successful, more so in the United States than in this country.

Douglas and Blomfield put forward the startling claim that 60% of the babies born in Great Britain in 1946 were potted within a fortnight of birth. This is at variance with the results in the present study, in which 30% of children began their training under the age of 3 months, and conflicts also with the tendency towards even later training in the U.S.A. described in the series of Davis and Havighurst (1946), Huschka (1943), and Klatskin (1952).

A further discrepancy is seen when the time of onset of training of enuretics is considered. Whereas Douglas and Blomfield found they had begun training later than the average, Huschka discovered the converse was true among her problem children, but she admitted the absence of "normal" controls. In the present series it was found that 72% of children had begun their training under the age of 9 months irrespective of whether they later became enuretic or not.

The period between birth and 10 months has been termed "early" by Huschka, and is included among her criteria for coercive training. This viewpoint has been accepted by virtually all psychiatrists up to the present day, although controls had not been studied; Prugh (1954), almost alone among them, separated early training from coercive methods, but even he found a high correlation between them. Huschka was, however, on more certain grounds when she specified the various punitive measures, both physical and psychological, adopted by many mothers, and included them among her criteria for coercive toilet training.

Whatever the nature of training, many variables are involved, including parental attitudes and aspirations, social prejudices, environmental factors, and maternal psychopathology, but the number of children studied in this investigation precluded consideration of these factors, important though they are; and, furthermore, made it impossible to determine the personality of each child in an adequate manner. Whatever the conscious or unconscious motives behind the method of training adopted by the mother, coercion was admitted in this survey in 38% of first-born enuretics but in a smaller percentage of later-born enuretics, dry siblings, and controls. In all groups the earlier the training started the more likely was it found to be conducted strictly, so that one might expect enuresis to be seen most commonly in those children who were trained below the age of 3 months; yet the converse was found to be the case, and most enuretics were discovered among those who began to be trained later.

Although only a minority of children had been trained strictly, this is not to deny that there may be some indirect relationship between strict training and enuresis, because resistance was met with twice as often in the enuretics receiving strict training as in those trained leniently. On the other hand, so many enuretics resisted who had been trained leniently that the part which strictness plays is an uncertain one, and suggests that it

is the resistance shown by a child at 1–1½ years of age rather than the timing or method of training which bears a closer connexion with enuresis.

Resistance was also noted in a relatively small number of dry siblings and controls, so that bed-wetting cannot be said to be its only outcome ; encopresis is even more closely related to it, and Huschka has shown that some behaviour problems may be an alternative undesirable reaction to coercion. But even in these dry children resistance has been shown to be related to a delay in sphincter control of about four months ; it is interesting to speculate whether some were on their way to becoming enuretic or encopretic but lacked the genetic factor (Hallgren, 1957) involving autonomic imbalance which would allow these conditions to develop.

The question to which no certain answer can be provided is the cause of the resistance encountered, particularly in many of the enuretics of this series. It is commonly believed that the mother is to blame, and this is probably true in so far as coercive measures play their part, but most children accept such training without demur and with no obvious side-effects. It may be the inborn personality of the child, in whom aggression and negativism are prominent features, which is more important than rigidity of method. But whichever interpretation is correct, toilet training is conducted so smoothly and effectively in the majority of children, whether enuretic or not, that it cannot be regarded as more than a contributory factor in some cases. On the evidence provided, little support can be given to those who maintain that, just as acquired (or onset) enuresis is largely determined by psychological stress after a child has become dry at night, so enuresis may persist from birth onwards because of the stress of coercive training.

Summary and Conclusions

A retrospective inquiry concerning toilet training was undertaken into 165 " wet " families comprising 225 enuretic children and 174 dry siblings, and the findings were compared with 174 " dry " families containing 384 children as controls. The results were as follows.

1. The age at which " potting " began was virtually the same in the enuretics, dry siblings, and controls (30% under 3 months, 42% between 3 and 9 months, and 28% over 9 months). It was concluded that the time of beginning training bears no relation to the problem of enuresis.

2. Strict methods were adopted in a minority of children, but were more prevalent if training began below the age of 3 months and more common in enuretics who were first-born or " only " children ; nevertheless, enuresis was found less often among those trained very early. Later-born enuretics were not trained more strictly than their dry siblings or the controls. For these reasons it is doubtful whether coercive training is an important factor in the production of enuresis.

3. Children trained in the later period (over 9 months) were handled leniently as a rule, but no difference in this respect was found between the enuretic and control groups, indicating that lax methods were likewise not more conducive to enuresis.

4. Strict training was more often associated with resistance, both active and passive, in all children. Enuretics resisted much more often than the controls even if training had been lenient ; most resistance was encountered if potting began after 3 months of age. It is inferred that this resistance is more closely related to enuresis than early training, but coercive methods played some part in producing it.

5. Early training seemed to lead to earlier sphincter control, but if resisted at any training period some delay occurred not only in enuretics but in dry children as well. Possible reasons for this delay and for the resistance apparently causing it have been tentatively put forward.

It was concluded that, while toilet training has no fundamental bearing on the causation of enuresis, resistance to training is often a contributory factor.

My thanks are due to Dr. Stuart Morrison, of the M.R.C. Social Medicine Research Unit, for statistical and other valuable help, and to Dr. Doyne Bell for his comments.

References

Anderson, F. N. (1930). *Amer. J. Dis. Child.*, **40**, 591.
Bakwin, H. (1949). *J. Pediat.*, **34**, 249.
Bostock, J., and Shackleton, M. G. (1951). *Med. J. Aust.*, **2**, 110.
—— —— (1952). Ibid., **1**, 357.
—— —— (1956). Ibid., **1**, 1042.
Davis, A., and Havighurst, R. J. (1946). *Amer. sociol. Rev.*, **11**, 698.
Despert, J. L. (1944). *Psychosom. Med.*, **6**, 294.
Douglas, J. W. B., and Blomfield, J. M. (1958). *Children under Five*. Allen and Unwin, London.
Hallgren, B. (1957). *Acta psychiat. scand.*, **32**, Suppl. 114.
Huschka, M. (1943). *Psychosom. Med.*, **5**, 254.
Klatskin, E. H. (1952). *Amer. J. Orthopsychiat.*, **22**, 52.
Prugh, D. G (1954). *Ann. N.Y. Acad. Sci.*, **58**, 355.
Stockwell, L., and Smith, C. K. (1940). *Amer. J. Dis. Child.*, **59**, 1013.

SOME OBSERVATIONS ON SALIVARY SECRETION AND FLUID ABSORPTION BY MOUTH

BY

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The secretion of saliva in normal healthy subjects is under nervous control, and there is no evidence of a specific hormonal mechanism. In the resting state the output of saliva is at a low level, but a marked increase occurs when the gland is activated as the result of a wide variety of reflexes, which may be unconditioned or acquired.

Substances placed in the mouth initiate the unconditioned salivary reflex. The stimulus may be produced by inedible objects and be purely of a mechanical nature, in which case the afferent pathway is by the lingual, buccinator, and palatine branches of the fifth nerve, and the pharyngeal branches of the vagus. Movements of the tongue and jaw have similar effects. Edible substances produce their effect by stimulating the taste fibres of the chorda tympani, and of the glosso-pharyngeal nerve.

Mechanical stimulation of the lower end of the oesophagus causes an increase in salivary secretion by means of the oesophago-salivary reflex. Similarly, the introduction of food into a gastrostomy produces a salivary response by the gastro-salivary reflex. Both these responses depend on the integrity of the vagi.

Salivary secretion which occurs when the mouth is empty is due to a wide variety of acquired reflexes. The

thought, taste, smell, or sight of food initiates these responses in which the higher cerebral centres play an essential part.

With such a complex system of reflexes it is obvious that measurement of normal salivary secretion is a matter of some difficulty, and is subject to many pitfalls. When estimating the resting secretion, the presence of apparatus in the mouth will give misleading results, since mechanical stimulation of the oral cavity gives rise to active salivary secretion. The method employed by Becks (1939) to measure resting secretion consists in obtaining specimens in a beaker which has been placed in contact with the lower lip, the patient leaning forward to allow all saliva to drip into the vessel. This method is subject to obvious criticisms, since saliva may be swallowed and oral breathing will cause evaporation. Spealman (1943), using a similar method, has attempted to gain greater accuracy in estimating the resting secretion by ensuring that specimens were obtained between meals, at the same time each day, and in patients who were not supervised and who were in a state of mental quiet.

The results obtained by these methods, however, show wide variation in the level of secretion in different subjects, and in the same subject when specimens have been obtained on different occasions. These variations apply not only to estimations of resting secretion but also to the active secretion obtained when the salivary reflexes have been stimulated by the chewing of paraffin gum (Wainwright, 1939).

The object of this paper is to record some observations made on salivary secretion in two patients, each of whom had been subjected to a somewhat unusual surgical procedure. During the course of these observations certain other features pertaining to fluid absorption by the mouth have been noted and are recorded and discussed.

Case 1

A married woman aged 47 was admitted to hospital on April 18, 1958, suffering from carcinoma of the middle third of the oesophagus. In spite of some difficulty in swallowing solid food her nutrition was good and she was not dehydrated.

On May 5 the entire thoracic oesophagus was excised, the cardiac orifice closed, and a gastrostomy established. The cervical oesophagus was exposed on the left side of the neck and delivered so as to establish a complete oesophageal fistula just below the medial end of the clavicle. This operation was the preliminary stage of complete oesophageal reconstruction. An adhesive ileostomy bag was fitted over the opening of the cut end of the oesophagus so that all salivary secretion, together with any fluids taken by mouth, could be collected and measured accurately.

Fig. 1 shows the salivary output for the first 16 days after operation. From the first to the sixth day fluids were not given by mouth, and the volume accumulating in the ileostomy bag represented the total salivary secretion. During this period the patient was given continuous intravenous glucose-saline. From the seventh to the sixteenth day various types of fluid (orange and lemon squash, milk, and water) were given by mouth in known quantities and on different days to study the effect of these as stimulants of salivary secretion. The volume of secretion was measured by subtracting the amount taken by mouth from that accumulating in the ileostomy bag.

It will be seen that during the first and second days after operation the total output of saliva was 45 ml. and 60 ml. respectively. This low output was attributed partly to dehydration, and partly to pre-operative medication and post-operative sedation. On the third day, when the patient no longer showed any clinical signs of dehydration, the volume of secretion rose steeply to 450 ml. and thereafter fell gradually to a level of 120 ml. during the sixth day after operation.

On different occasions during the next 10 days, while the patient was being fed through the gastrostomy, various fluids were given by mouth, and the effect of these on salivary output was recorded. It will be seen that the giving of orange squash, milk, or even water stimulates salivary secretion, but that lemon drinks provided by far and away the most marked response, the volume secreted reaching a level of 545 ml. in 24 hours. On the days when water was given the volume of secretion varied between 85 and 120 ml., giving an average daily secretion of 110 ml.

Case 2

A man aged 72 suffering from carcinoma of the lower end of the oesophagus was admitted to hospital on September 11, 1958, in a state of severe malnutrition and gross dehydration. The operative procedure carried out was identical to that described in Case 1. Specimens from the cut end of the oesophagus were collected exactly as previously.

Fig. 2 shows the results in this case, observed over a period of 19 days after operation. During the first eight post-operative days the patient was instructed to take sips of water by mouth as and when he felt inclined, and his fluid intake was measured. In addition, he was given intravenous glucose-saline. It will be seen that in the first two days after operation 140 and 120 ml. less fluid was

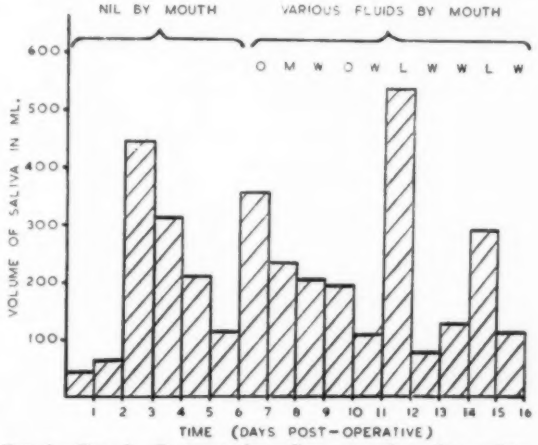

FIG. 1.—Case 1. Post-operative salivary secretion. It was low in the two days after operation, followed by a marked increase on the third day, when the patient was well hydrated. Note low secretion when water is given by mouth, and the marked response to lemon. O=Orange squash. L=Lemon squash. M=Milk. W=Water.

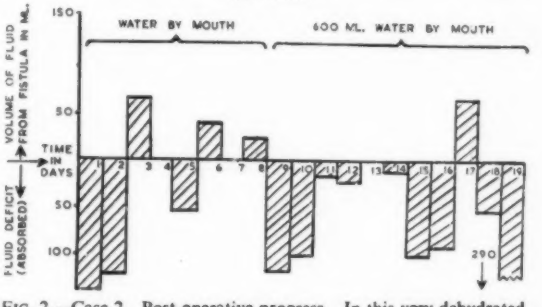
WATER BY MOUTH
600 ML. WATER BY MOUTH
VOLUME OF FLUID FROM FISTULA IN ML.
150
50
TIME IN DAYS
50
100
FLUID DEFICIT (ABSORBED)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
290

FIG. 2.—Case 2. Post-operative progress. In this very dehydrated patient the volume of fluid obtained from the oesophageal fistula was less than the volume of fluid taken by mouth on 12 out of 19 days. It is suggested that these readings indicate fluid absorption from the mouth or cervical oesophagus.

obtained from the oesophageal fistula than the patient had actually taken by mouth. A similar deficit occurred on the fifth day, and on only three occasions during the first eight days was more fluid obtained from the fistula than was taken by mouth.

At first it was thought that the deficiency was due to leaking from the ileostomy bag, although no leak was apparent. It was therefore decided to observe him for a further period, and from the 8th to the 19th postoperative day he was given sips of water amounting to 600 ml. a day, and the volume obtained from the oesophageal fistula measured. It will be seen that on only one occasion was more fluid obtained from the fistula than was given by mouth. On all other occasions a deficit varying from 10 to 290 ml. was apparent. On the 13th day complete balance was obtained. During this entire period of observation the patient continued to be in a state of dehydration.

Discussion

Collection of Saliva

The method of obtaining specimens of salivary secretion described is an unusual one, and the opportunity of obtaining them occurred quite fortuitously during the course of a staged operation for excision of carcinoma of the oesophagus and subsequent oesophageal reconstruction.

The establishment of a complete cervical oesophageal fistula ensured that no salivary secretion was lost, and obviates the criticism directed at other methods of collection where saliva may be swallowed accidentally. No apparatus was present in the mouth, so that unwanted mechanical stimulation of the oral cavity did not occur, and in addition there was no loss of salivary secretion by evaporation as the result of mouth-breathing. The fact that the vagi were completely severed distal to the origins of their cardiac branches ensured that gastrostomy feeding did not affect secretion by initiating the gastro-salivary reflex; although, of course, psychic stimuli could still occur.

Estimations of secretions were carried out over a considerable period of 16 days in one case and 19 days in the other. After the patients had recovered from the operative procedure they were able to sit up in bed, read, talk to other patients, and be quite unaware that estimations of salivary secretion were in fact in progress. In these respects the conditions under which salivary secretion was studied were as nearly normal as possible.

Volume of Secretion

Normal salivary secretion is said to amount to between 1,000 and 1,500 ml. in 24 hours (Best and Taylor, 1955), this figure being a combination of both active and resting secretion during the period of the day. From the work of Spealman (1943) the estimated resting secretion varies between 220 and 838 ml. a day, while from that of Wainwright (1939) the estimated active secretion can vary from 408 to 4,560 ml.

It will be noticed that in Case 1, although the patient's condition was good, on no occasion did the total daily salivary output rise above 545 ml. In the five days in which no stimuli were applied, the average resting secretion was only 110 ml. in the 24 hours. When active secretion was induced by giving lemon drinks the highest daily output was only 545 ml. It would appear, therefore, that previous estimations of the volume of salivary secretion have been very much too high, probably due to the method of collection of the specimens.

It will be recalled that salivary secretion has been considered an effective neutralizing agent to gastric secretion, but, in view of the present volumetric estimations, this neutralizing effect must be less important than was thought.

Water Balance

It is generally considered that the salivary glands play a part in the regulation of the water balance of the body. When the water content of the body is adequate saliva is secreted continuously, while in conditions of dehydration the dry furred tongue indicates that salivary secretion has been reduced with a view to conserving much-needed body fluid. This function is exemplified in Case 1 in that, during the first two days after operation, when the patient was dehydrated, the total salivary output a day averaged 52.5 ml., but when dehydration was combated adequately by intravenous infusion salivary secretion rose on the third day to a level of 450 ml. In certain respects, therefore, the salivary glands respond as do the kidneys in maintaining fluid balance.

Fluid Absorption by Mouth

An extensive search of the literature has failed to produce any work on fluid absorption from the mouth, although the absorption of drugs from the oral cavity seems to be a well-established practice. While Case 1 has shown that salivary output is greatly diminished during dehydration, Case 2 goes a stage further in that the findings suggest that fluid was actually absorbed from the mouth or the cervical oesophagus. During a period of 19 days during which the patient was sipping measured quantities of water by mouth, the volume of fluid retrieved from a perfectly sealed oesophageal fistula was on most occasions less than the volume of fluid that had been swallowed. This deficit varied from 10 to 290 ml. a day. A fluid deficit was actually present on 12 of the 19 days, and, as has been emphasized, this patient was in a condition of extreme dehydration. The explanation of this can only be that fluid was absorbed from the mouth or the cervical oesophagus.

It is interesting to recall the progress of surgical patients who are under treatment with intravenous fluid combined with gastric suction. From personal observation over some years it has appeared that patients sipping fluid by mouth while gastric aspiration is being continued become hydrated more quickly than does the patient to whom no fluid is given by mouth or where fixed quantities have been inserted through the intragastric tube. The findings in Case 2 may well explain this observation, in that in these circumstances fluid may be absorbed by mouth and supplement the intravenous therapy already being administered.

Summary

Estimations of salivary output have been described in two cases of special interest.

The low volume of resting secretion has been emphasized and the response to various stimulations has also been recorded. The daily output of saliva is very much less than that previously accepted.

Fluid absorption from the mouth or cervical oesophagus has been shown to occur in cases of extreme dehydration.

References

Becks, H. (1939). *J. dent. Res.*, **18**, 431.
Best, C. H., and Taylor, N. B. (1955). *The Physiological Basis of Medical Practice*, 6th ed. Baillière, Tindall and Cox, London.
Spealman, C. R. (1943). *Amer. J. Physiol.*, **139**, 225.
Wainwright, W. W. (1939). *J. dent. Res.*, **18**, 441.

EFFECT OF MOTHERS' SMOKING HABITS ON BIRTH WEIGHT OF THEIR CHILDREN

BY

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It has been reported that when pregnant rats and rabbits are exposed to tobacco smoke their offspring weigh less than those of control animals (Essenberg, Schwind, and Patras, 1940; Schoeneck, 1941). A similar observation has been made in respect of pregnant women. Simpson (1957) collected data over a three-year period from American maternity hospitals and found that the incidence of premature births (those weighing 5½ lb.—2.5 kg.—or less) among women who smoked was double that among non-smokers and increased fairly regularly with the amount smoked. No explanation was offered for this observation, but it is clear from the data that age, parity, and social circumstances had little to do with it.

The subject seemed to be of sufficient importance to require further investigation, particularly since Simpson's report left a number of important questions unanswered. For example, it did not indicate whether the low birth weight was attributable to retardation of foetal growth or to early onset of labour.

The present paper gives the results of an inquiry into the effect of smoking upon the pregnancies of 2,042 women delivered in six Birmingham maternity hospitals during the summer of 1958.

Material

In order to obtain accurate information about smoking during pregnancy, it was thought desirable to limit the inquiry to recent deliveries. Two social workers visited six maternity hospitals in Birmingham at frequent intervals over a period of five months. At each visit they completed a questionary for every woman delivered in the hospital since the previous visit. An obstetrical history was recorded in the ward day-room from the hospital record card and a smoking history at the bedside from the mother. In addition each woman was asked what her weight was immediately before she became pregnant. Non-Europeans and women who had had twin births were excluded.

Results

The sample of 2,042 women contained 1,155 who did not smoke at any time during their pregnancy (women who had never smoked or had given up smoking before they conceived), 181 who smoked during the early months of pregnancy but gave up later (all but 7 of them before the end of the fifth month), 38 who stopped early in pregnancy but later began to smoke again, and 668 who smoked regularly throughout pregnancy. Since the data were not complete in every detail for every woman, it will be found that the numbers in these four categories vary a little from table to table.

Birth Weight

The basic data of the investigation are presented in Table I and Fig. 1. Infants of mothers who smoked regularly throughout pregnancy were on the average more than 6 oz. (170 g.) lighter than infants of those who never smoked during pregnancy, referred to subsequently as non-smokers (6.93 lb. and 7.33 lb. respectively—a difference of 0.40 ± 0.06 lb.). There were only 38 women who gave up smoking early in pregnancy but later began to smoke again, so no significance can be attached to the mean weight of their infants. There was no difference between weights of infants of non-smokers and of women who gave up early in pregnancy and did not begin to smoke again. This suggests that the influence of smoking upon birth weight may possibly be greater during the second than during the first half of pregnancy; but again the numbers are rather small. The analysis which follows is concerned only with the non-smokers (1,155) and the regular smokers (668), women in the two small intermediate categories being excluded.

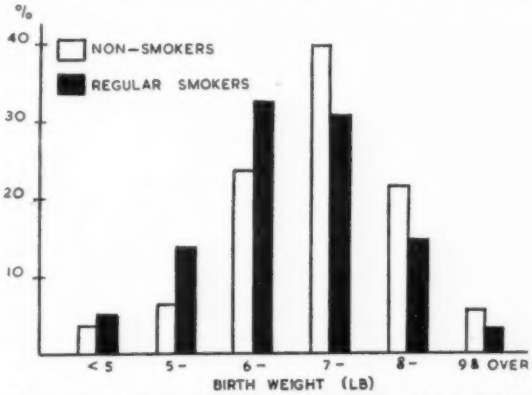

FIG. 1.—Birth weight of infants related to their mothers' smoking habits.

Table II shows that the mean weight of infants of heavy smokers (10 or more cigarettes a day) was less than that of infants of light smokers (fewer than 10

TABLE II.—*Mean Birth Weight (lb.) of Infants Related to Maternal Smoking Habits During Pregnancy*

Sex of Infant	Non-smokers	Regular Smokers		Total
		<10 Cigs. a Day	10 or More Cigs. a Day	
Male ..	7·43 (607)	7·18 (187)	7·05 (165)	7·32 (959)
Female ..	7·23 (539)	6·74 (163)	6·67 (147)	7·04 (849)
Total ..	7·33 (1,146)	6·98 (350)	6·87 (312)	7·18 (1,808)

TABLE I.—*Percentage Distribution of Birth Weights of Infants Related to Maternal Smoking Habits during Pregnancy*

Smoking Habits During Pregnancy	Birth Weight (lb.)								
	<4	4–	5–	6–	7–	8–	9+	Total	Mean±S.E.
Never smoked*	1·7 (19)	1·9 (22)	6·5 (74)	23·8 (273)	39·8 (456)	21·5 (241)	5·4 (61)	100 (1,146)	7·33±0·03
Gave up early in pregnancy ..	0·6 (1)	2·2 (4)	6·7 (12)	26·7 (48)	38·3 (69)	18·3 (33)	7·2 (13)	100 (180)	7·36±0·29
Gave up but later began again	2·6 (1)	2·6 (1)	10·5 (4)	28·9 (11)	34·2 (13)	15·8 (6)	5·3 (2)	100 (38)	7·11±0·59
Smoked regularly	2·7 (18)	2·4 (16)	13·9 (92)	32·3 (214)	30·8 (204)	14·8 (98)	3·1 (20)	100 (662)	6·93±0·05

* Women who never smoked during pregnancy are referred to as "non-smokers" in the figures and in subsequent tables.

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cigarettes a day). This was true of both male and female infants. The influence of smoking on birth weight was so pronounced that male infants of regular smokers were appreciably lighter than female infants of non-smokers—a reversal of the usual sex difference in weight.

Duration of Gestation

The possibility that the low birth weight of infants of women who smoked during pregnancy was attributable to shortening of the duration of gestation was examined. Intravenous nicotine is known to release antidiuretic hormone, which can be found in human urine after smoking (Burn, 1951), so it is not impossible that smoking might have an oxytocic effect.

To explore this possibility the duration of gestation was examined in smokers and non-smokers. Since the question considered was whether tobacco smoking induces early onset of labour, it was of course necessary to exclude from the comparison pregnancies which had been terminated by surgical induction and elective caesarean section. There was no substantial difference between duration of gestation of smokers and of non-smokers (Table III). That tobacco does not have an oxytocic effect was confirmed by the observation that, with one interesting exception, whatever the duration of gestation the mean birth weight of children born to smokers was always less than that of children born to non-smokers (Fig. 2). The fact that gestations of less than 260 days did not conform to this general pattern lends some support to the suggestion made in the preceding section, that the influence of smoking upon birth weight may lie mainly in the later months of pregnancy. Further confirmation of the finding that smoking has little or no effect upon duration of gestation is provided in Table IV, in which it is shown that for a given birth weight the percentage of mothers who were smokers bore little relation to duration of gestation. On the other hand, at each duration of gestation there was a striking inverse relation between birth weight and percentage of smokers. For gestations of 290 days and over, 57% of the mothers of infants weighing 6 lb. (2.7 kg.) or less were smokers, compared with 17% of those of infants weighing 9 lb. (4 kg.) or more. Again the shorter durations of gestation (less than 260 days) were exceptional.

Maternal Weight

Although the matter does not appear to have been scientifically investigated, it is common knowledge that tobacco has an adverse effect upon appetite and that smokers who give up the habit tend to put on weight. Since the birth weight of an infant is directly related to the weight of its mother (McKeown and Record, 1957) the possibility has to be considered that the observed relationship between smoking and birth weight

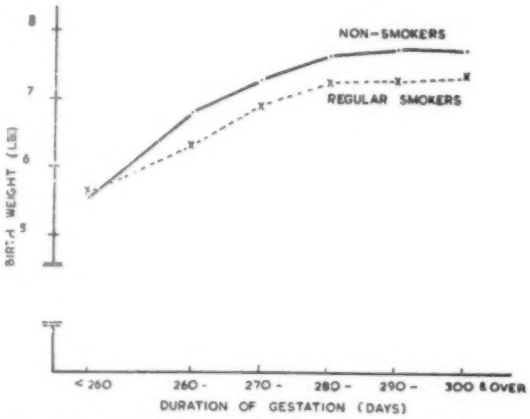

FIG. 2.—Birth weight related to duration of gestation and maternal smoking habits.

may be due to the effect of smoking upon maternal nutrition. It was indeed found (Table V) that smokers weighed significantly less than non-smokers. (Maternal weights were based on mothers' statements about their weights immediately before pregnancy, but there seems to be no reason why they should be biased in relation to smoking habits.) However, the difference—less than 4 lb. (1.8 kg.)—hardly seems sufficient to account for the difference in birth weight, since dietary deficiencies have little influence upon birth weight unless they are severe

TABLE III.—*Percentage Distribution of Non-smokers and Regular Smokers According to Duration of Gestation**

Gestation (Days)	<250	250–	260–	270–	280–	290–	300+	Total	Mean ± S.E.
Non-smokers	3·7 (33)	2·7 (24)	9·2 (81)	26·9 (237)	39·1 (345)	14·9 (131)	3·5 (31)	100 (882)	279·9 ± 1·5
Regular smokers	5·5 (30)	5·1 (28)	10·5 (57)	24·6 (134)	35·8 (195)	14·3 (78)	4·2 (23)	100 (545)	278·5 ± 1·7

* Pregnancies terminated by surgical induction or elective caesarean section are excluded.

TABLE IV.—*Percentage of Mothers who Were Smokers Related to Birth Weight and Duration of Gestation (all Deliveries)*

Gestation (Days)	Birth Weight (lb.)					Total
	<6	6–	7–	8–	9+	
<260	45·8 (83)	41·0 (39)	42·1 (19)	(6)	(1)	43·2 (148)
260–	46·9 (49)	42·6 (61)	22·4 (58)	16·7 (12)	—	35·6 (180)
270–	50·9 (53)	34·8 (158)	28·2 (174)	27·1 (70)	21·4 (14)	32·6 (469)
280–	57·1 (35)	40·1 (167)	27·6 (286)	26·2 (164)	17·9 (39)	31·3 (691)
290+	57·1 (21)	48·3 (87)	28·8 (170)	27·3 (110)	16·7 (36)	32·8 (424)
Total	51·5 (241)	40·2 (512)	28·0 (707)	26·2 (362)	18·9 (90)	33·3 (1,912)

TABLE V.—*Percentage Distribution of Mothers According to Their Weight Before Pregnancy*

Mother's Weight (st.)*	<7	7–	8–	9–	10–	11–	12+	Total	Mean ± S.E.
Non-smokers	1·7 (19)	14·5 (158)	30·2 (330)	28·8 (314)	13·8 (151)	6·8 (74)	4·1 (45)	100 (1,091)	9·29 ± 0·04
Regular smokers	3·2 (20)	19·2 (121)	32·2 (203)	24·6 (155)	13·5 (85)	5·1 (32)	2·4 (15)	100 (631)	9·02 ± 0·05

*14 lb.

(Thomson, 1951). This view is supported by the observation that when the mothers were grouped according to their weights the infants or non-smokers were heavier than the infants of smokers for each maternal weight group (Table VI). At the same time, of course, for both smokers and non-smokers birth weight increased regularly with maternal weight.

TABLE VI.—*Mean Birth Weight (lb.) of Infants Related to Mother's Weight (st.)*

Mother's Weight (st.)	Non-smokers (a)	Regular Smokers (b)	Difference (a–b)
<7 ..	6·50 (19)	6·05 (20)	+0·45
7– ..	6·87 (156)	6·46 (121)	+0·41
8– ..	7·24 (328)	6·80 (201)	+0·44
9– ..	7·24 (313)	7·23 (153)	+0·01
10– ..	7·50 (149)	7·14 (84)	+0·36
11+ ..	7·82 (117)	7·59 (46)	+0·23
Total ..	7·33 (1,082)	6·92 (625)	+0·41

Maternal Age and Parity

It is necessary now to inquire whether the relation between birth weight and maternal smoking habits is influenced by maternal age or parity. It is known that birth weight increases with parity fairly consistently to the third birth rank (McKeown and Gibson, 1951), and it is not unlikely that smoking habits may be related either to parity or to age (with which parity is closely correlated). The data showed no consistent change in smoking habits with age, but there was a marked and rather unexpected relationship with parity (Table VII).

TABLE VII.—*Percentage of Mothers who were Smokers Related to Age and Parity (All Deliveries)*

Age	Parity*				Total
	1	2	3	4+	
<25	27·8 (724)	42·5 (181)	41·9 (43)	50·0 (10)	32·0 (958)
25–	31·2 (285)	31·8 (132)	34·7 (49)	40·5 (42)	31·3 (508)
30–	40·4 (99)	32·6 (92)	38·5 (39)	50·0 (64)	32·5 (294)
35+	31·8 (44)	23·3 (60)	35·3 (34)	42·2 (102)	34·6 (240)
Total	29·9 (1,152)	35·1 (465)	37·6 (165)	44·5 (218)	33·3 (2,000)

* In assessing parity, stillbirths were included.

Although the change was greatest for young mothers, the proportion of women who smoked regularly throughout pregnancy increased fairly regularly with parity for each age group. Under 25 years of age 43.4% of the women in their third or later pregnancy were regular smokers, compared with only 27.8% of the primiparae. Clearly this can have played no part in determining the relationship between smoking and birth weight. Indeed, since both the proportion of smokers and birth weight increased with parity, it will, if anything, have decreased the overt effect of the one upon the other. This point is underlined in Table VIII.

TABLE VIII.—*Mean Birth Weight (lb.) Related to Maternal Parity*

Parity	Non-smokers	Regular Smokers	Total
1	7·27 (684)	6·83 (342)	7·12 (1,026)
2+ ..	7·43 (462)	7·03 (319)	7·27 (781)
Total ..	7·33 (1,146)	6·93 (661)	7·19 (1,807)

For both primiparae and multiparae the infants of smokers weighed less than the infants of non-smokers. The effect of smoking is so marked that it can apparently override the usual pattern of parity and birth weight, for the infants of primiparous non-smokers were heavier than the infants of multiparae who smoked.

Complications of Pregnancy and Labour

Apart from reports by Mgalobeli (1931) and Athayde (1948) that women who work in the tobacco industry are more subject to abortion and stillbirth than women in the general population, there does not appear to be any reference in the literature to the effect of tobacco upon the frequency of complications of pregnancy and labour in the human female. So far as the present inquiry is concerned there was nothing to suggest that cigarette smoking was related to complications of pregnancy. The incidence of toxaemia and of ante-partum and post-partum haemorrhage was much the same for smokers and for non-smokers (Table IX), and there was no great difference in the frequency with which delivery was effected by caesarean section or with obstetrical forceps (Table X).

TABLE X.—*Type of Delivery*

	Caesarean Section	Forceps	Other	Total
Non-smokers ..	5·5 (63)	6·8 (79)	87·7 (1,013)	100% (1,155)
Regular smokers	5·5 (37)	5·1 (34)	89·4 (597)	100% (668)

However, smoking had one noticeable effect upon the course of pregnancy. It was shown in Table III that the tobacco habit had little effect upon the length of gestation when it was naturally determined—that is, when labour began spontaneously. But the proportion of pregnancies in which labour was surgically induced was substantially lower among the women who smoked throughout pregnancy than among those who did not smoke (Table XI). The difference, although small, was highly significant. Smoking apparently provides a measure of insurance against surgical interference with the normal course of pregnancy. This is not altogether unexpected. Suspected disproportion is a common reason for surgical induction, and, as we have shown, the size of the foetus is influenced by maternal smoking habits.

TABLE XI.—*Percentage of Pregnancies in Which Labour was Surgically Induced**

Sex of Infant	Percentage of Surgical Inductions		Difference ± S.E. (a–b)
	Non-smokers (a)	Regular Smokers (b)	
Male ..	20·0 (610)	16·4 (353)	3·6 ± 2·6
Female ..	20·7 (545)	13·3 (315)	7·4 ± 2·6
Total ..	20·3 (1,155)	15·0 (668)	5·3 ± 1·8

* Includes elective caesarean section.

Foetal Complications

The question whether maternal smoking habits have any effect upon the foetus other than upon its birth

TABLE IX.—*Percentage Incidence of Complications of Pregnancy*

	Toxaemia	Threatened Abortion	Ante-partum Haemorrhage	Post-partum Haemorrhage	Other*	None	Total
Non-smokers	5·8 (67)	1·8 (21)	1·9 (22)	2·3 (27)	7·7 (89)	80·4 (929)	100 (1,155)
Regular smokers ..	3·3 (22)	1·9 (13)	2·8 (19)	2·1 (14)	6·6 (44)	83·2 (556)	100 (668)

* Albuminuria from causes other than toxaemia, severe oedema, pyelitis, etc.

weight is clearly of considerable importance. There is no answer to this question in the literature, and the evidence in the present inquiry is inconclusive. Minor foetal abnormalities are irregularly and incompletely recorded in hospital records (from which the data were obtained), and major abnormalities are relatively uncommon. A much larger sample would therefore be required to uncover any but the grossest effects.

When stillbirths and deaths within the first 24 hours were grouped together, mortality among the infants of smokers was a little higher than among those of non-smokers (30 and 23 per 1,000 total births respectively). Since the total number of deaths was only 47, this could easily be a chance effect. In the same way, although the incidence of major malformations was rather higher among smokers than among non-smokers (15 and 11 per 1,000 respectively), the numbers were too small to permit any conclusion to be drawn (Table XII).

TABLE XII.—*Major Malformations*

Malformation	Non-smokers	Regular Smokers
Anencephalus (with or without spina bifida)	6	2
Hydrocephalus (with or without spina bifida)	4	3
Spina bifida alone	—	1
Renal conditions	2	—
Imperforate anus	—	2
Exomphalos	1	1
Congenital heart	—	1
Total	13	10
Number of pregnancies	1,155	668
Incidence per 1,000 births	11	15

Smoking appeared to have no influence upon the incidence of foetal asphyxia, which was 70 per 1,000 for smokers and 81 per 1,000 for non-smokers.

Discussion

In this investigation it is shown that smoking during pregnancy reduces the birth weight of the infant. The reduction in weight is by no means trivial. Infants of mothers who smoked throughout pregnancy weighed on the average 6 oz. (170 g.) less than infants of mothers who did not smoke. This was much more than the difference between male and female infants and between first and later births. It appeared to be great enough to lower significantly the incidence of surgical induction among smokers.

Since the effect of smoking upon birth weight is not due to a shortening of gestation, it must be attributed to a direct retardation of foetal growth. It is not difficult to suggest possible explanations for this. It is conceivable, for example, that tobacco might have a direct pharmacological action on the foetus, since the foetal heart rate increases when a pregnant woman smokes a cigarette (Sontag and Wallace, 1935; Doerfel, 1952). An even more credible explanation is that smoking during pregnancy may restrict the placental circulation, retarding the growth of the foetus by limiting its blood supply. In most normal adults smoking causes a peripheral vasoconstriction which may last for half an hour or longer, and is associated with a rise in both systolic and diastolic blood pressures and a measurable decrease in the temperature of fingers and toes (Simon, Iglauer, and Braunstein, 1954: Eckstein, Wood, and Wilkins, 1957; Roth and Shick, 1958). Moreover, there is some evidence that women are more sensitive than men to these effects (Friedell, 1953). It is therefore quite possible that vasoconstriction, repeated ten or more times a day, might have an appreciable effect upon the nutrition of the foetus, particularly during the later months of pregnancy.

If the effect of smoking on birth weight is as considerable as this inquiry indicates, it is evident that it must make a substantial contribution to the frequency of "premature births," defined according to weight. Moreover, it suggests a possible explanation for the observation that there has been no significant decline in the incidence of premature births in a period when obstetric services have improved considerably. In the same period the proportion of women who smoke has risen steadily, and this must have contributed in some degree to the relative constancy of the proportion of infants born at low weights.

Summary

Obstetrical and smoking histories were recorded for 2,042 pregnant women delivered in six Birmingham maternity hospitals during the summer of 1958.

The mean weight of infants of mothers who smoked regularly throughout pregnancy was 6 oz. (170 g.) less than that of infants of mothers who never smoked during pregnancy (6.93 lb. and 7.33 lb. respectively). This was more than the difference in weight between male and female infants and between first and later births. It was sufficient to lower significantly the incidence of surgical induction among smokers.

The effect of smoking upon birth weight was unrelated to maternal weight, age, and parity, or to the complications of pregnancy. It was not due to shortening gestation (brought about by early onset of labour). It is concluded, therefore, that smoking during pregnancy substantially retards foetal growth.

It is with pleasure that I acknowledge my indebtedness to the obstetricians at Dudley Road, the Queen Elizabeth and St. Chad's Hospitals, and at Heathfield Road, Lordswood, and Marston Green Maternity Hospitals. I also thank Miss Ida Giles and Mrs. Eileen Armstrong, who interviewed the patients and helped to sort the data.

References

Athayde, E. (1948). *Brasil-méd.*, **62**, 237.
Burn, J. H. (1951). *Brit. med. J.*, **2**, 199.
Doerfel, G. (1952). *Z. ges. inn. Med.*, **7**, 227.
Eckstein, J. W., Wood, J. E., and Wilkins, R. W. (1957). *Amer. Heart J.*, **53**, 455.
Essenberg, J. M., Schwind, J. V., and Patras, A. R. (1940). *J. Lab. clin. Med.*, **25**, 708.
Friedell, M. T. (1953). *J. Amer. med. Ass.*, **152**, 897.
McKeown, T., and Gibson, J. R. (1951). *Brit. J. soc. Med.*, **5**, 98.
—— and Record, R. G. (1957). *J. Endocr.*, **15**, 410.
Mgalobeli, M. (1931). *Mschr. Geburtsh. Gynäk.*, **88**, 237.
Roth, G. M., and Shick, R. M. (1958). *Circulation*, **17**, 443.
Schoeneck, F. J. (1941). *N.Y. med. J.*, **41**, 1945.
Simon, D. L., Iglauer, A., and Braunstein, J. (1954). *Amer. Heart J.*, **48**, 185.
Simpson, W. J. (1957). *Amer. J. Obstet. Gynec.*, **73**, 808.
Sontag, L. W., and Wallace, R. F. (1935). Ibid., **29**, 77.
Thomson, A. M. (1951). *Brit. J. Nutr.*, **5**, 158.

A group of senior public health administrators from 25 European countries including the United Kingdom participated in a travelling seminar in the U.S.S.R. from September 15 to October 17, sponsored by the Regional Office for Europe of the World Health Organization. The seminar was designed to acquaint its members with public-health administration in various parts of the U.S.S.R. Visits were made to various medical institutions, medical schools, research establishments, and to health services in cities, in factories, in rural areas, as well as in sanatoria and spas. The itinerary included Moscow, Leningrad, Minsk, Kiev, Yalta, and Stalingrad. Professor M. KACKPRZAK, Rector of the Medical Academy of Warsaw, acted as consultant during the seminar (W.H.O. Euro/103).

VENTRICULAR TACHYCARDIA ASSOCIATED WITH THYROTOXICOSIS

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Though Parry, in 1786, described irregular, as well as forcible and rapid, action of the heart in exophthalmic goitre, it was not until the development of electrocardiography that the nature of the arrhythmias associated with thyrotoxicosis could be clearly distinguished. Auricular fibrillation accounts for most of these arrhythmias—20% in a series of 1,000 cases described by Ernstene (1938). Auricular flutter (Phillips and Anderson, 1927), heart-block (Kremer and Laplace 1936), and bundle-branch block (Digilio, 1938) have been described but are rare. Ventricular tachycardia does not appear to be a recognized arrhythmia in thyrotoxicosis.

In a series of 107 cases of ventricular tachycardia (Armbrust and Levine, 1950) there were no cases attributed to thyrotoxicosis. Coronary disease accounted for the majority, but rheumatic heart disease and congenital heart disease were responsible for some. In 13 cases no aetiological cause was found.

Parkinson and Papp (1947) described a condition termed "repetitive ventricular paroxysmal tachycardia"—runs of ventricular tachycardia interspaced between runs of sinus rhythm. One of their patients, aged 32, with this condition over a period of two and a half years, was found to be mildly thyrotoxic when seen 10 years later, though she then had a normal electrocardiogram with sinus rhythm.

We here describe a case of ventricular tachycardia in a woman with thyrotoxicosis.

Case Report

A woman aged 31 was admitted to hospital complaining of severe palpitations for 24 hours. The attack had been sudden in onset and was associated with some dyspnoea and general weakness. She had noticed similar attacks in the past two months, but they had been less severe, lasting only a few hours. There was no history of rheumatic fever, nor had she been taking digitalis.

On examination there was no oedema or finger-clubbing, and her neck veins were not distended. The pulse rate was over 200 a minute at the apex and her blood-pressure was 100/60. Slight cardiac enlargement and fine crepitations at the lung bases were present, but no hepatic enlargement. An E.C.G. revealed ventricular tachycardia (Fig. 1).

Procainamide, 1 g., was given orally and repeated in four hours. After this treatment the electrocardiogram showed normal sinus rhythm (Fig. 2).

Further investigation did not reveal any evidence of organic heart disease; however, she did have a persistent tachycardia with a sleeping pulse rate of 90–100, and moist warm hands, with some tremor. Her thyroid gland was enlarged and the clinical diagnosis of thyrotoxicosis was confirmed by radioactive iodine studies. Her thyrotoxicosis was controlled by potassium perchlorate, and no further attacks of palpitations occurred in the subsequent nine months.

*Now at the Liverpool Stanley Hospital.

Discussion

No recognized cause of ventricular tachycardia could be found in this case. Ischaemic heart disease appears unlikely in view of the patient's age, sex, and normal electrocardiogram after the attack. There was no clinical evidence of rheumatic or congenital heart disease. She had not received digitalis.

One might argue that this patient had idiopathic ventricular tachycardia unconnected with thyrotoxicosis, but as the attacks ceased after control of the thyrotoxicosis it seems reasonable to incriminate thyrotoxicosis as the cause of the tachycardia.

It is well recognized that thyroxine acts directly on the myocardium. McIntyre (1931) produced tachycardia in denervated dogs' hearts by thyroxine, and experimental evidence suggests that it increases the sensitivity of cardiac muscle to adrenaline. Rosenblum, Hahn, and Levine (1933) produced thyrotoxicosis in animals by thyroid feeding and then studied the effects of adrenaline infusions on their cardiac rhythm by electrocardiogram. Paroxysmal ventricular tachycardia was produced in all animals with doses of adrenaline too small to alter the cardiac rhythm of normal controls. If such a mechanism is responsible for arrhythmia in thyrotoxicosis, it is difficult to explain why ventricular tachycardia is so rare. Furthermore, Burn, Gunning, and Walker (1957) have shown that adrenaline inhibits the production of experimental auricular fibrillation. It seems unlikely, therefore, that adrenaline sensitivity plays a major part in the arrhythmias of thyrotoxicosis.

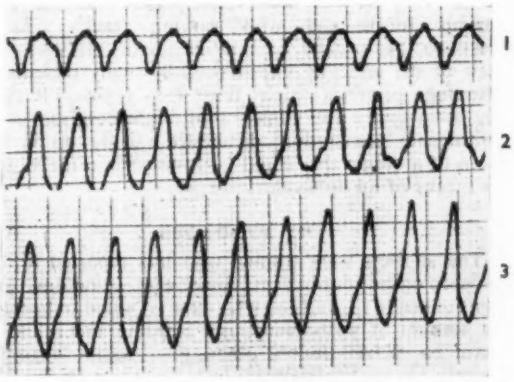

FIG. 1.—E.C.G. on admission, showing ventricular tachycardia in standard leads.

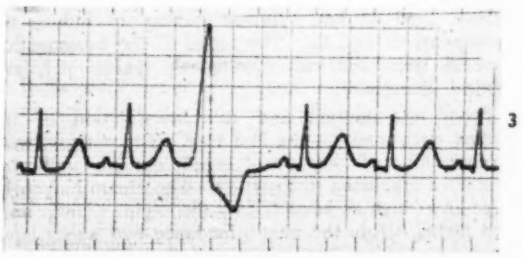

FIG. 2.—Standard lead 3 following procainamide, showing sinus rhythm.

An alternative mechanism of thyroid hormone acting directly on the myocardium, shortening the refractory period, warrants consideration.

Summary

A case history is described of a woman aged 31 with thyrotoxicosis who developed ventricular tachycardia. No recognized cause for this arrhythmia could be found.

Our thanks are due to Dr. M. Toohey and Dr. Raymond Greene for permission to publish this case, and to Dr. David Rideout for his help.

REFERENCES

Armbrust, C. A., and Levine, S. A. (1950). *Circulation*, **1**, 28
Burn, J. H., Gunning, A. J., and Walker, J. M. (1957). *J. Physiol. (Lond.)*, **137**, 141.
Digilio, V. A. (1938). *Amer. Heart J.*, **15**, 116.
Ernstene, A. C. (1938). *Amer. J. med. Sci.*, **195**, 248.
Kremer, D. N., and Laplace, L. B. (1936). *Amer. Heart J.*, **11**, 227.
McIntyre, M. (1931). *Amer. J. Physiol.*, **99**, 261.
Parkinson, J., and Papp, C. (1947). *Brit. Heart J.*, **9**, 241.
Phillips, J., and Anderson, J. P. (1927). *J. Amer. med. Ass.*, **89**, 1380.
Rosenblum, H., Hahn, R. G., and Levine, S. A. (1933). *Arch. intern. Med.*, **51**, 279.

SENILE VAGINITIS TREATED WITH DIENOESTROL CREAM

BY

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Senile vaginitis has been treated with oestrogens in various forms and with varying results. Local treatment has usually been by means of pessaries. In view of the difficulty experienced by many patients in inserting pessaries high into the vagina, it was suggested that a full clinical trial might be given to an oestrogenic preparation, dienoestrol, made up in the form of a cream that could be inserted into the vagina by means of an applicator.

The Investigation

The subjects were women who had reported to the gynaecological out-patient clinic with symptoms and signs of senile vaginitis or who were admitted to hospital on account of post-menopausal bleeding and found to have no pelvic lesion other than senile vaginitis. Twenty-one patients were investigated. Their ages varied from 41 to 71, and the interval that had elapsed since the menopause ranged from 1 to 23 years. In 10 cases the interval was more than 10 years. The patient aged 41 had received radium to induce the menopause at age 31. The scope of the investigation covered bacteriological, cytological, vaginal *p*H, and clinical changes.

Pelvic examination and full investigation of the vagina were made at the first visit. The patients were given a tube of dienoestrol cream and an applicator and were instructed in their use. The cream had to be injected as high as possible into the vagina nightly until two nights before the next attendance two weeks later. The investigation was repeated and each patient was told to continue using the cream until the tube was empty, which was usually after 16 applications. The third visit was two to four weeks later, and if treatment was still required a second tube was provided and the fourth visit arranged in a further four weeks. If clinical improvement with the first tube had been satisfactory, patients were informed that no further treatment was necessary but they would be asked to report at some future date.

Signs and Symptoms.—In nine of the patients post-menopausal bleeding was the main symptom, three had vaginal discharge, four had symptoms of prolapse and discharge, one had frequency of micturition, and four had irritation of the vulva. All patients showed in varying degree the typical speckling of the vaginal mucosa, particularly in the upper half. Generally, the mucosa was shiny, thin, and atrophic. The state of the epithelium was estimated by Mack's test, which indicates the amount of glycogen present in the vaginal cells by the uptake of iodine. Grade 1 indicates no glycogen present and grade 4 its presence in full amount.

Method.—Swabs were taken from the upper part of the vagina and complete reports of the direct films and cultures were given by the bacteriologist.—The *p*H was estimated at each visit by means of the bromo-cresol purple capillator with a range from *p*H 5.2 to 6.8 The intervals elapsing between the first and final visits varied from three months to one year, except for one patient who reported at one month quite cured but who failed to return for assessment 10 months later.

Results

One tube of cream produced a marked improvement in the state of the vaginal mucosa in 14 patients, a second tube was required in six, and a third tube was necessary in one. Nearly all patients stated that they felt very comfortable, and one even volunteered that life was "heaven." The assessment one-plus (+) was given to the four patients showing a *p*H of 6 or above at the final visit, although they were symptom-free. The two-plus assessment (++) was used for those who showed a clinical cure and where the *p*H was less than 6. In these 17 cases the vaginal mucosa was pink, appeared to be thicker, and showed no evidence of speckling. Vaginal examination was much easier and caused no pain, although treatment in some cases had been given 10 and 11 months previously. In no case was there any withdrawal bleeding.

Bacteriologically the cases were interesting. The pathogens included *Staph. albus*, *Staph. aureus*, Haemolytic streptococcus (group A), *Escherichia coli*, and *Proteus vulgaris*, the majority of which were probably contaminants. Their presence had no effect on the results (Table I).

TABLE I.—*Ocurrence of Pathogens in Relation to Results*

Present at first visit Absent at final ,,	6	.. ..	++5 +1
Present at first visit ,, ,, final ,,	4	Same pathogen at both visits in 1 ..	++3
		Different ,, ,, ,, ,, ,, 3 ..	+1
Absent at first ,, Present at final ,,	5	.. ..	++5
Absent at first ,, ,, ,, final ,,	6	.. ..	++4 +2

The occurrence of non-pathogens showed a different pattern; in 11 cases where they were present at the beginning none were found at the final visit. The details are given in Table II.

TABLE II.—*Summary of Occurrence of Non-pathogens in Relation to Results*

Present at first visit, Absent at final	11	++9, +2
Present at first, ,, final	5	++3, +2
Absent at first, Present at final	2	++2
Absent at first, ,, final	3	++3

The presence or absence of red cells, pus cells, and Döderlein bacilli is shown in Table III.

TABLE III

	Present First Visit Absent Final Visit	Present First and Final Visits	Absent First Visit Present Final Visit	Absent First and Final Visits
Red cells	9	4	2	6
Pus	6	4	4	7
Döderlein bacilli	1	0	4	16

Pus Cells.—It will be noted that some pus cells were present in eight patients at the final visit though these all showed a clinical cure. Red cells were found in six patients at the final visit, having been present in four of these at the first attendance.

pH.—At the first visit the average *p*H was 6.4, varying from 5.8 to 7, but at the last visit it was 5.6, varying from 5.2 to 6.8.

Mack's Test.—At the first visit 7 were grade 1, 13 grade 2, and 1 grade 3. At the final visit all showed improvement, and in some this was very marked, with grade 4 classification.

Discussion

The bacteriological findings confirm the accepted views on the bacteriology of the senile vagina and senile vaginitis. The bacteria are not the cause but the result of the vaginitis, which can be cured for an indefinite period by local oestrogen therapy.

In the post-menopausal patient, circulating oestrogens are reduced but not absent, and are sufficient to maintain the healthy senile vagina. If the weakened oestrogen defence is overcome, and vaginitis results, the low oestrogen level in the post-menopausal patient may be unable to restore the vaginal mucosa to normal, but, as the local tissue response to oestrogens is not usually impaired, local oestrogen therapy can restore its vitality. Thereafter the reduced oestrogen levels of the post-menopausal patient can maintain the vagina in a clinically healthy state for an indefinite period in the absence of any local adverse factor such as a pessary or a severe degree of prolapse. The ease of application, duration of cure, and absence of withdrawal bleeding make local dienoestrol cream therapy a safe and worthwhile treatment for senile vaginitis.

Summary

Twenty-one patients with senile vaginitis were fully investigated, and then treated with dienoestrol cream.

In 17 a marked clinical improvement occurred, in 14 of them after only one tube. This was found to be maintained when examinations were made at intervals up to one year.

The presence of pathogens did not appear to have any effect. In six patients, who were completely cured, no pathogens were present at the first visit but were found at the final visit.

As non-pathogenic organisms decreased, improvement was noted.

In no case did withdrawal bleeding occur.

We are grateful to Dr. J. C. J. Ives, who read all the bacteriological results, and to his staff who prepared the films and cultures. The dienoestrol cream, which contained 0.01% dienoestrol in an absorptive cream base, was supplied by Ortho Pharmaceutical Limited, to whom we express our thanks for help and co-operation. Our thanks are due to Dr. H. Stirling, in whose wards some of the patients were investigated.

Preliminary Communications

Pre-erythrocytic Stages of Human Malaria Parasites: Plasmodium malariae

The pre-erythrocytic stages of *Laverania falciparum*, *Plasmodium vivax*, and *P. ovale* have been demonstrated (Shortt *et al.*, 1948, 1949; Garnham *et al.*, 1954). Only the pre-erythrocytic stages of *P. malariae* among the human malaria parasites remained to be found. This last parasite has proved to be the most difficult to handle and its pre-erythrocytic cycle by far the most elusive. The prime criterion for success in these experiments is the successful infection of hundreds of susceptible mosquitoes and their maintenance for over two weeks. On 17 separate occasions I have failed to achieve this aim under conditions which might be considered as exceptionally favourable; that is, the simultaneous possession of large numbers of susceptible mosquitoes (*Anopheles gambiae*), a sufficiency of chimpanzees, and a reasonable proportion (20%) of the local children infected with *P. malariae*.

With the use of the methods outlined by Bray (1957) success has eventually been obtained.

The Experiment

A 7-year-old female child showing a reasonable gametocyte infection of *P. malariae* "fed" 450 *A. gambiae*. These mosquitoes were well infected, and sporozoites appeared in the salivary glands 14 days after feeding. Sixteen days after feeding, the salivary glands of 110 *A. gambiae* were inoculated intravenously into Chimpanzee No. 55, and the salivary glands of another 110 *A. gambiae* were inoculated into Chimpanzee No. 61, which had been splenectomized eight days previously.

Liver pieces were removed from No. 61, 8 and 10 days after inoculation; and from No. 55, 9 days after inoculation. On the 11th day after inoculation No. 55 was killed and a large amount of the liver was taken.

Sections of the liver were prepared and the presence of pre-erythrocytic schizonts of *P. malariae* was demonstrated in the material. The schizonts bear a close similarity to those of *P. inui*, which have been demonstrated by Garnham (1951), except that the host parenchyma-cell nucleus or nuclei are enlarged. A full description of the experiment will be published at a later date.

This work was supported by a grant, E-2178 (C1), from the National Institutes of Health, U.S. Public Health Service. I am greatly indebted to Dr. R. W. Burgess for supplying and maintaining the mosquitoes and for his valuable help in their dissection. I gladly acknowledge the help of Dr. A. E. Gunders for his assistance in the dissection of mosquitoes and for the time he gave

unstintingly during the laparotomies upon the chimpanzees. I wish to thank Mr. Boife Freeman, senior technician, for the preparation of the histological sections.

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REFERENCES

Bray, R. S. (1957). *Amer. J. trop. Med. Hyg.*, **6**, 514.
Garnham, P. C. C. (1951). *Trans. roy. Soc. trop. Med. Hyg.*, **45**, 45.
—— Bray, R. S., Cooper, W., Lainson, R., Awad, F. I., and Williamson, J. (1954). *Brit. med. J.*, **1**, 257.
Shortt, H. E., Fairley, N. H., Covell, G., Shute, P. G., and Garnham, P. C. C. (1949). Ibid., **2**, 1006.
—— Garnham, P. C. C., Covell, G., and Shute, P. G. (1948). Ibid., **1**, 547.

Medical Memoranda

Prevention of Peptic Ulceration During Corticosteroid Therapy

That the oral administration of cortisone and its analogues predisposes to peptic ulceration is no longer in dispute. In a study reported by Kammerer *et al.* (1958), 36 out of 117 rheumatoid arthritic patients receiving oral corticosteroid therapy were found to have radiological evidence of peptic ulceration. Treatment of the affected patients included cortisone, hydrocortisone, prednisone, "medrol" (6-methyl prednisolone), and triamcinolone. Of special interest was the finding that 31 of the 36 ulcers were gastric and the majority were on the greater curvature. This finding, also noted by others, suggested that oral cortisone-like steroids do not activate the factors that commonly lead to peptic ulceration, but have a separate contribution to make.

We have found the incidence of dyspepsia remarkably low in patients receiving controlled adrenal stimulation therapy (corticotrophin) for prolonged periods (West, 1957). This, coupled with the finding that there is not an increased incidence of peptic ulceration in patients with Cushing's syndrome (Kirsner and Palmer, 1952), suggests that orally administered cortisone-like steroids may affect the stomach wall *directly*. Such a local action might be avoided in the following ways:

1. By giving antacids with the steroid. This has been done routinely by many physicians ever since cortisone became available, and has not prevented the formation of ulcers.

2. By giving an anticholinergic drug that will reduce gastric secretory activity (Carbone and Liebowitz, 1958). This may be of value even though the consensus of opinion is that oral corticosteroid therapy does not raise the level of free hydrochloric acid and pepsin above the normal. A preliminary trial at this centre of prednisolone combined with an anticholinergic drug ("ultracortenol"+"antrenyl") in patients who already had dyspepsia on oral prednisolone has proved encouraging enough to justify a controlled trial.

3. By coating the prednisolone tablet so that it will not dissolve in the stomach. Experience with the use of such a tablet is reported below.

4. By giving the corticosteroid parenterally.

We have found that prednisolone given as "delta cortril suspension intramuscular" is suitable for long-term depot therapy and that it is of real value in the treatment of patients who have severe gastric symptoms (West, 1958).

ENTERIC-COATED PREDNISOLONE TABLETS

The cortisone type side-chain, which is common to all the physiologically active cortisone-like steroids at present in use, is readily destroyed by certain intestinal bacteria. This can be shown *in vitro*, and is found to be the case *in vivo* if an enteric-coated prednisolone tablet does not dissolve rapidly after leaving the stomach. We found that if a patient was changed from plain prednisolone tablets to an enteric-coated tablet that had too thick a coating his symptoms relapsed. The failure to absorb all the prednisolone could be confirmed by changes in the urinary excretion of total 17-hydroxy-corticosteroids. Tablets very heavily coated may, of course, be passed unchanged.

After a number of failures we found that an enteric-coated prednisolone tablet was absorbed normally, so we proceeded to give it to a series of patients who were complaining of dyspepsia while receiving plain prednisolone tablets.

Fifteen patients were treated. Of these, three thought the tablets had less effect on their arthritis, so they reverted to plain tablets before the effect upon their gastric symptoms could be assessed. One patient found her gastric symptoms worse. She had at the same time symptoms arising from diverticulitis, so was not really a suitable patient for the trial. The remaining 11 patients all claimed a major relief of gastric symptoms and found the antirheumatic effect unchanged. Conventional antacid therapy was being given before the changeover. Subsequently most of these patients were able to dispense entirely with the antacids. All 11 patients were suffering from rheumatoid arthritis. Two were receiving a high dose of prednisolone for complicating polyarteritis and a third had recently had a haematemesis. The findings justified the change to enteric-coated tablets, but the case for their use would have been stronger had the trial been "controlled." As it was, preliminary studies of enteric-coated capsules and tablets had provided evidence of the value of such coating so that subsequently it was not regarded as ethical to withhold them from the patients with dyspepsia referred to above in order to have a control group.

Thanks are due to Pfizer Ltd., who prepared the enteric-coated prednisolone tablets for us and made available a generous supply, and to Dr. E. V. B. Morton, of Boots Pure Drug Co. Ltd., who supplied enteric-coated capsules and tablets for the preliminary studies.

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REFERENCES

Carbone, J. V., and Liebowitz, D. (1958). *Metabolism*, **7**, 70.
Kammerer, W. H., Freiberger, R. H., and Rivelis, A. L. (1958). *Arth. and Rheum.*, **1**, 122.
Kirsner, J. B., and Palmer, W. L. (1952). *Amer. J. Med.*, **13**, 615
West, H. F. (1957). *Ann. rheum. Dis.*, **16**, 322.
—— (1958). Ibid., **17**, 273.

After several meetings between representatives of the medical profession from all parts of the country, the International Diabetes Federation, a predominantly lay organization, has decided to form a Medical Section. Membership will be open to any doctor who is interested, but non-medical members will be eligible for election only with the consent of the Section's executive committee. It is proposed to hold at least one medical meeting a year when special lectures and discussions will be arranged. (*News Bulletin*, July, 1959, International Diabetes Federation.)

Reviews

GADDUM'S "PHARMACOLOGY"

Pharmacology. By J. H. Gaddum, M.R.C.S., L.R.C.P., Sc.D., F.R.S. Fifth edition. (Pp. 587+xvi; illustrated. 42s.) London, New York, Toronto: Oxford University Press. 1959.

Pharmacology is indeed a difficult problem for an author at the present time. The steady flow of new drugs makes it tempting to stick to the general principles of their action and not to consider them in detail. But if this is done the book ceases to be a work of reference, for which purpose a large section of readers expect to find it of value. The publishers of this book point out that it is a remarkable achievement on the part of the author to have included all new drugs of importance without increasing the text by more than 25% since the first edition in 1940. There are, however, drawbacks, for in consequence the book is condensed and is not always easy for a hasty student to read. In Edinburgh, where Professor Gaddum has taught, the teaching of pharmacology is planned more sensibly than in some other universities, for during part of the course the student is in the wards where he can watch the drugs being used. The course is also longer, and for both reasons the student has more chance to assimilate the volume of information with which he is presented.

The outstanding features of the book are the reliability of the information contained in it and the judicious care with which that information has been selected. In both respects Gaddum's *Pharmacology* remains what it has been for many years—a model, and a standard by which other authors may measure their efforts. It is evident that hitherto the author has maintained a constant watch on successive editions, and it will be a matter of interest to see for how long he can continue to do so. If there are indeed practitioners of medicine who like to browse on medical literature in the evening, this is an attractive and informative volume to keep on the small table beside the armchair.

J. H. Burn.

AVIATION MEDICINE

Aviation Medicine. Selected Reviews. Edited by Clayton S. White, W. Randolph Lovelace II, and Frederic G. Hirsch. (Pp. 305+vii; illustrated. 70s.) London: Pergamon Press. 1958.

Aviation medicine has always been hard to define, and, while some may use the term in a narrow sense to mean only those conditions which are specific to aviation, others may use it to embrace all conditions that may occur in flight, whether they are rare on the ground or not. Many intermediate definitions are possible also. This book is not concerned with clinical medicine, but otherwise the widest possible definition has been adopted, and some title such as "Selected Papers on Biophysical Method" would carry a clearer meaning in the United Kingdom. Even so, such a title would not indicate the scope of the book, which consists of the following twelve reviews: (1) spirometric method; (2) high-speed cine-photography; (3) measurement of atmospheric ozone; (4) methods and apparatus for the study of stress reaction and metabolic changes; (5) dosimetry of ionizing radiations; (6) some technical developments applicable to problems in pathology; (7) temperature-measuring technique; (8) analysis of respiratory gases; (9) aerosols—physical properties, instrumentation, and technique; (10) transducers of transformer type; (11) spectrometric methods of gas analysis; and (12) gas-sampling method.

The reviews are a condensed source of information for guidance of those working in the concerned fields, and refer particularly to instrumentation, experimental method, and technique. Much valuable detail of available method is given, along with many useful hints and tips to ensure that the apparatus behaves as well as it ought to. For this purpose the book is good, though necessarily the standard of, and approach to, the various sections are uneven.

About a quarter of the book is concerned with techniques for the respiratory physiologist. Of particular interest is the review regarding gas analysis by emission spectroscopy, and all who use, for example, the Lilley Anderson nitrogen meter should know of this section, where many practical details, not generally available, are given. Clinicians will be disappointed, however, that nowhere in the book are there descriptions of techniques for the timed fast vital capacity or for maximum breathing capacity. The other sections will be of value to workers in the relevant specialized fields and may stimulate interest in many others not yet familiar with them, for the presentation of the subject-matter is generally attractive and the book is easy to read.

The volume is well produced and has many clear diagrams. Each review has an extensive bibliography, which can be criticized in that in some sections recent work is omitted. As might be expected, there is a tendency to describe American equipment and omit mention of equally useful British and Continental equipment. These criticisms do not, however, detract a great deal from its value, and it should be available to all senior staff concerned with biophysical research.

H. L. Roxburgh.

DR. LOGAN CLENDENING

Logan Clendening Lectures on the History and Philosophy of Medicine. Eighth series. *Disease and Destiny. Logan Clendening.* By Ralph H. Major. (Pp. 49; illustrated. $2.) Lawrence: University of Kansas Press. 1958.

This little book contains the eighth series of (two) Logan Clendening lectures on the history and philosophy of medicine. The course is now delivered annually in the University of Kansas; and the previous lectures, by historians of medicine from the U.S.A., Canada, and Britain, have attracted large audiences and, when printed, have appealed to a wide circle of readers. In his first lecture, on "Disease and Destiny," Dr. Major shows how disease, when widespread, may affect the destiny of nations, and how the ill-health of one important individual may likewise influence the course of history. As examples of the first he mentions such devastating epidemics as the Plague of Athens, the Black Death, and the typhus fever which decimated Napoleon's army in Russia; while the second is exemplified by the physical and mental troubles of Nietzsche, Woodrow Wilson, and Lenin.

The second lecture is a brief biography of Logan Clendening himself, and none was better qualified to undertake the task of writing it than Dr. Ralph Major, who was Clendening's close friend and colleague for 25 years, and who succeeded him as professor of the history of medicine in 1949. He tells us that Dr. Logan Clendening was one of the most colourful and picturesque figures of his time in American medicine. Born in Kansas City of Scottish parents in 1884, he graduated M.D. in 1907, and, after a period of further

study and travel, returned to become a leading physician and professor of medicine in the University of Kansas. His fame as a teacher was equalled only by his skill as an author. His book entitled *The Human Body* (1927), written mainly for non-medical readers, became so popular that the circulation rose to half a million copies. Clendening was then asked to write a daily column, which at the time of his death in 1946 was appearing in 383 newspapers throughout the U.S.A. When he undertook this work he thought it better to withdraw from his private practice, but he continued his academic duties. His column was always informative and often witty, and full of sound philosophy and common sense. He also made valuable contributions to the history of medicine, and his splendid collection of early medical works was bequeathed to the University of Kansas, where it is a cherished possession. It is housed in the Hixon Laboratory, a fine building which Mrs. Clendening (Dorothy Hixon) presented to the university in 1939. The library is known to medical historians throughout the world.

The enthusiasm and dynamic energy of Logan Clendening have done much to raise medical history to its present position as a broad cultural basis of modern medicine. Professor Major, already familiar to so many as the author of *Classic Descriptions of Disease, Hippocrates and the Isle of Cos*, and especially of his two-volume *History of Medicine*, has paid a graceful and well-merited tribute to one who deserves to be remembered and honoured as an erudite historian of medicine, as a devoted and inspiring teacher, and as a cordial and sympathetic friend.

DOUGLAS GUTHRIE.

ATLAS OF OBSTETRICS

A Baby is Born. The Picture Story of Everyman's Beginning. Prepared by Maternity Center Association. French translation by Monique Beljanski; Spanish translation by Dr. Percy Boland. (Pp. 66; illustrated. $6.) New York: Maternity Center Association. 1957.

The subtitle adequately describes the scope of a book which consists essentially of a series of illustrations. Each is accompanied by an elaborate caption which offers explanation in terms of both anatomy and physiology. The text is, however, so concise that the lay person (for whom the work is intended) may find some difficulty in assimilating and understanding all the facts unless he or she receives some guidance. So far as Great Britain is concerned, the obvious place for this atlas is as a supplement to the instruction given to expectant mothers. For such a purpose it should prove of the greatest help. The illustrations are quite outstanding, many of the photographs of sculptures by Dr. Robert L. Dickinson and Abram Belski having a three-dimensional quality. The reproduction is superb, and it is doubtful whether more simple, accurate, and pleasing illustrations of the anatomy of conception, pregnancy, and labour can be found elsewhere. Any teacher of the fundamentals of obstetrics, to medical students and nurses as well as to the laity, would find them useful.

T. N. A. JEFFCOATE.

Textbook of Comparative Histology, by Warren Andrew, of Indiana School of Medicine, is a well-illustrated systematic account of the microscopic structure of invertebrates and vertebrates, intended primarily for students of biology and zoology and pre-medical students. It is available from the Oxford University Press (pp. 652+xix; £6).

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

National Library of Medicine Catalog, 1958. (Pp. 1,031+vii. $17.50.) Washington: Library of Congress. 1959.

Heavy Metals and the Brain. By John N. Cumings, M.D., F.R.C.P. (Pp. 161+vii; illustrated. 32s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

Pain. Problems pertaining to the Transmission of Nerve Impulses which give rise to Pain. By W. Noordenbos. (Pp. 182; illustrated. 42s. 6d.) Amsterdam, London: Elsevier Publishing Company. 1959.

The Anastomoses between the Leptomeningeal Arteries of the Brain. Their Morphological, Pathological and Clinical Significance. By Henri M. Vander Eecken, M.D. (Pp. 160+xvi; illustrated. 57s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

La Tuberculose des Houilleurs. By Jacques Prignot. (Pp. 327; illustrated.) Brussels: Editions Arscia S.A. 1959.

Current Problems in Allergy and Immunology. Papers dedicated to Béla Schick on the occasion of his 80th birthday. Edited by William Kaufman. (Pp. 992+xxiv; illustrated. Sw. Fr. 60; $14.40.) Basle, New York: S. Karger. 1959.

Odd Man Out: Homosexuality in Men and Women. By Eustace Chesser. With a foreword by Kenneth Walker. (Pp. 192. 12s. 6d.) London: Victor Gollancz Ltd. 1959.

Experiment Perilous. Physicians and Patients Facing the Unknown. By Renée C. Fox. (Pp. 262. $5.) Glencoe, Illinois: Free Press. 1959.

Strahlenbelastung Strahlengefährdung und Strahlenschutz in der Röntgendiagnostik. Edited by Günter Liess, M.D. Assisted by Ernst Dörffel, M.D., and Dr. Wolfgang Degner. (Pp. 64. DM. 3.10.) Berlin: VEB Verlag Volk und Gesundheit. 1959.

Grundriss der Bakteriologie und Serologie. By Dr. Hans Heinrich. (Pp. 134+xi; illustrated. DM. 18.70.) Jena: VEB Gustav Fischer Verlag. 1959.

Sonderausschuss Radioaktivität Bundesrepublik Deutschland. Zweiter Bericht. (Pp. 117. DM. 12.60.) Stuttgart: Georg Thieme Verlag. 1959.

Microbiology Yesterday and Today. Edited by Vernon Bryson. (Pp. 122. $4.) Rutgers: Institute of Microbiology, The State University. 1959.

Proceedings of the Tenth Annual Conference on the Nephrotic Syndrome. Edited by Jack Metcoff, M.D. (Pp. 282+xiii; illustrated.) New York: National Kidney Disease Foundation. 1959.

Röntgendiagnostik des Magen-Darmkanals. By Dr. R. Prévôt and Dr. M. A. Lassrich. (Pp. 346+xi; illustrated. DM. 119.) Stuttgart: Georg Thieme Verlag. 1959.

Progress in Hematology. Vol. II. Edited by Leandro M. Tocantins, M.D. (Pp. 290+vi; illustrated. $9.75.) London, New York: Grune and Stratton. 1959.

Pathologie und Klinik des Salz- und Wasserhaushaltes. By Professor Dr. Edmund Kerpel-Fronius. (Pp. 678; illustrated.) Budapest: Verlag der Ungarischen Akademie der Wissenschaften. 1959.

Schizophrenia. An Integrated Approach. Edited by Alfred Auerback, M.D. (Pp. 224+viii. $5.50.) New York: Ronald Press Company. 1959.

Les Régulations Physiologiques. Essai de Révision Biométrique du Problème de l'Homéostasie. By Eugène Schreider. (Pp. 89.) Paris: Office International de Documentation et Libraire. 1958.

Grundriss der Physiologischen Chemie für Veterinärmediziner, Humanmediziner und Biologen. By Martin Schenck, M.D., Ph.D., and Erich Kolb. Third edition. (Pp. 333+xv. DM. 23.80.) Jena: VEB Gustav Fischer Verlag. 1959.

Statistical Methods in Biology. By Norman T. J. Bailey, M.A., D.S.C. (Pp. 200+ix. 25s.) London: English Universities Press Ltd. 1959.

The Catarrhal Child. A Symposium. (Pp. 44; illustrated. 6s.) London, Edinburgh: Chest and Heart Association. 1959.

The Meaning of Poison. By Lloyd G. Stevenson, M.D. (Pp. 53. $2.) Lawrence, Kansas: University of Kansas Press. 1959.

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HEREDITY IN BREAST CANCER

Environmental causes of epithelioma, such as chronic exposure to radiation or to certain irritating substances like tar, are well established. Individual differences in susceptibility, which may be inborn, to these carcinogens scarcely need to be taken into consideration. Conversely there are examples of malignant tumours which arise on a hereditary basis in the absence of any obvious environmental peculiarity, as occurs in familial intestinal polyposis[1] and keratosis of palms and soles with oesophageal carcinoma.[2] Between these rare extremes the common types of cancer are to be accounted for. Among them, mammary carcinoma, which is the cause of death of one woman in every forty, is especially prevalent and worthy of investigation to find out how far it may be genetically determined.

This is done by studying families. With common diseases, however, there are special pitfalls to be avoided. The observation that many cases of breast cancer can sometimes be concentrated in one pedigree was first convincingly made by P. Broca,[3] and it has been repeated by many later investigators, but two points remained undecided. It was not clear, first, how much concentration in families should be attributed to chance coincidence of a common event, and secondly whether, if established, the familial susceptibility was a generalized tendency to cancer rather than one which was specific to breast cancer. Difficulty in arriving at the truth arose especially from the unsatisfactory nature of the information about the control families because of imperfect recording of morbidity rates. In this particular disease records of mortality are much more trustworthy than those of morbidity, and consequently recent surveys have been confined to the study of mortality statistics, comparing in this respect data from relatives of known patients with data from the general population. The most accurate techniques of family study were probably those used by L. S. Penrose and colleagues,[4] D. W. Smithers,[5] C. M. Woolf,[6] and V. E. Anderson and colleagues.[7] These investigators independently concluded that the risk of developing breast cancer is increased if a close relative has been affected, but that the risk of developing other types of malignant disease is unconnected. The increases noted by Anderson and colleagues,[7] however, were smaller than those recorded by previous investigators. A more recently published study by M. T. Macklin,[8] who used a slightly different but comparable method, has underlined the significance of the familial concentration of patients with breast cancer by comparison with mortality statistics from the general population. A new feature in this work was the use of one additional set of control families derived from patients selected for cancer in some other organ and another set derived from patients who were free from any malignant disease. Again, the same conclusions were reached with the additional safeguard here that no increase of deaths from breast cancer was noted among the relatives of patients in either control group.

Summarizing the consistent results of these recent inquiries, we find that the risk of occurrence of fatal breast cancer in sisters of affected patients is about three times as great as that for females in the general population. The incidence in mothers of such patients is about double that in the general population, and there is also a noticeably higher incidence in their grandmothers and in their female cousins. The increased risk is largely independent of whether the female relative is on the maternal or paternal side of the family, though some data have indicated an excess of affected maternal relatives. There is also an increased risk for male relatives; indeed, breast cancer in men is such a rare event that its occasional appearance in pedigrees of female cases is striking. This was clearly shown in O. Jacobsen's survey.[9] A number of further points stand out clearly. The risk is greater for unmarried than for married women. There is a tendency for the affected side, right or left, to be the same in a mother and daughter pair or in a pair of sisters.

What conclusions about causation can be drawn from such information as this? It is evident, in the first place, that a virus, such as the milk factor detected by J. J. Bittner[10] in mice, cannot be very significant in man. If it were prevalent, a strong predominance of affected maternal aunts and grandmothers, as opposed to paternal aunts and

[1] Dukes, C. E., *Ann. Eugen.* (*Lond.*), 1952, **17**, 1.
[2] Clarke, C. A., Howel-Evans, A. W., and McConnell, R. B., *Brit. med. J.*, 1957, **1**, 945.
[3] Broca, P., *Traité des tumeurs*, 1866, **1**, 149. Paris.
[4] Penrose, L. S., MacKenzie, H. J., and Karn, M. N., *Ann. Eugen.* (*Lond.*), 1948, **14**, 234.
[5] Smithers, D. W., *Brit. J. Cancer*, 1948, **2**, 163.
[6] Woolf, C. M., *Univ. Calif. Publ. publ. Hlth*, 1955, **2**, 265.
[7] Anderson, V. E., Goodman, H. O., and Reed, S. C., *Variables Related to Human Breast Cancer*, 1958, Minneapolis.
[8] Macklin, M. T., *J. nat. Cancer Inst.*, 1959, **22**, 927.
[9] Jacobsen, O., *Heredity in Breast Cancer*, 1946, Copenhagen.
[10] Bittner, J. J., *Amer. J. Cancer*, 1939, **36**, 44.
[11] Penrose, L. S., *Acta genet.* (*Basel*), 1953, **4**, 257.
[12] Gorer, P. A., in *Clinical Genetics*, 1953, London.

grandmothers, would have been expected. The same type of reasoning tends to exclude other cytoplasmic agents as likely causes. We have to postulate inherited predispositions for some women and men to develop cancer at particular sites. For mammary cancer we have to choose between a susceptibility determined by a number of genes and that determined by a single gene as the cause of precancerous hyperplasia. In familial intestinal polyposis the predisposition is a dominant trait caused by a rare autosomal gene. In the case of mammary carcinoma the predisposition, whether due to a single gene or multifactorial, must be very common. The higher incidence in sister pairs as compared with mother-and-daughter pairs suggests that, if a single autosomal gene is the origin, the trait would be recessive and be possessed by about 16% of all individuals,[11] though manifested almost exclusively in females. It is not at present possible to ascertain whether a person has such an inherited disposition or not, and the theory can be considered only as a rough descriptive approximation.

The pathological classification of the tumours observed in these surveys reveals a clearly defined range of conditions including spheroidal-celled carcinoma, adenocarcinoma, and scirrhous types. There is, however, no guarantee that they all have the same genetical basis. Some further information on this question may eventually be obtained from the study of breast cancer in identical twins[12]; very few of such cases have been so far recorded. In spite of these uncertainties the knowledge that an increased specific risk attends close relatives of known cases may be helpful in bringing patients to seek treatment at early and treatable stages of the disease.

THE STAPHYLOCOCCAL MENACE

When infection of clean operation wounds by antibiotic-resistant *Staphylococcus aureus* became a major problem about five years ago, almost all that was known about the habits of this organism was that it could survive and multiply in the noses of about half the normal population, that it could contaminate their skin and clothing, and that the strains isolated from outbreaks in hospitals frequently belonged to the same phage type. Despite the many papers that have been published in the intervening years, it cannot be said that we know very much more about the sources and methods by which this organism reaches operation wounds. Indeed, only three instances are known in which it has been possible to identify the individual from whom the organisms were probably derived. In two they were instrument nurses who were nasal carriers[1 2] and in one it was a surgeon who operated when he had a septic focus on his forearm.[3] But there must have been many other, unrecorded, cases in which it was impossible to find a carrier who could have been responsible.[4]

Even less is known of the origins of the small epidemics of wound infection occasionally seen in surgical wards in which it appears probable that the organisms reached the wound after operation. Often there are a sufficient number of carriers of the epidemic strain among the nurses to suggest that it is their organisms that reach the wounds, but transfer from septic wound to clean wound, directly on the hands of surgeon or nurse or indirectly on such vehicles as particles from the dressings, dust, blankets, and screens, is equally possible. Failure to identify the sources of the organisms and to trace the path by which they spread may well have been due to the assumption that they must have come from outside the patient, so that search for sources generally entailed looking for nasal carriers among hospital staff or for infected foci in the immediate vicinity of the patient. But the paper by Dr. R. E. O. Williams and colleagues published at p. 658 of the *Journal* this week shows clearly that in the great majority of post-operative infections, and indeed of superficial infections generally, the organisms did not come to the infected area directly from an outside source but from the nose of the patient himself.

In what must have been an exceedingly laborious investigation, requiring study of no fewer than 1,358 patients, it was found that, of the 722 who had had operations, 342 were not nasal carriers on admission nor did they become carriers while in hospital. Post-operative infection occurred in only seven, or 2.0%, of these patients. But, of the remaining 380, who were either nasal carriers on admission or became carriers, no fewer than 27, or 7.1%, became infected. The difference in incidence is striking, but even more so are the observations that 18 of the 27 had staphylococci of the same phage type in both wound and nose and that in all but three the organisms were known to have been present in the nose before infection developed. Somewhat similar results were obtained in an analysis of the incidence of septic lesions not connected with operations, 2.1% of the non-carriers and 6.9% of the carriers becoming

[1] Sompolinsky, D., Hermann, Z., Oeding, P., and Rippon, J. E., *J. infect. Dis.*, 1957, **100**, 1.
[2] Pennikett, E. J. K., Knox, R., and Liddell, J., *Brit. med. J.*, 1958, **1**, 812.
[3] McDonald, S., and Timbury, M. C., *Lancet*, 1957, **2**, 863.
[4] Barber, M., Wilson, B. D. R., Rippon, J. E., and Williams, R. E. O., *J. Obstet. Gynaec. Brit. Emp.*, 1953, **40**, 476.
[5] Ridley, M., *Brit. med. J.*, 1959, **1**, 270.
[6] Barber, M., and Burston, J., *Lancet*, 1955, **2**, 578.
[7] Hare, R., and Ridley, M., *Brit. med. J.*, 1958, **1**, 69.
[8] —— and Thomas, C. G. A., ibid., 1956, **2**, 840.

infected. The authors accordingly suggest that, in general, the first step in the production of any form of sepsis is parasitization of the nose by staphylococci. The second step is transfer of the organisms from the nose to the wound or other site that eventually becomes infected.

There seems to be little doubt that in the process of parasitizing the nose the epidemic types current in hospitals (which seem to be more capable of causing infection than most strains) are able to oust the strains which the patient carries in his nose on entry into hospital.[4] This process, moreover, seems to be facilitated if the patient is receiving antibiotics, for the epidemic types are almost uniformly resistant. For these reasons Williams and colleagues suggest that in order to prevent infections it may be necessary to prevent parasitization of patients' noses by hospital epidemic strains, perhaps by isolating the patient or applying antiseptic or antibiotic creams to the nose.

In these investigations the assumption was made that the only carrier site on the patient from which the organisms came was the nose, but the perineum may be equally if not more important.[5] For about 50% of nasal carriers are also perineal carriers and a by no means negligible proportion of the population (10%) are perineal carriers only, with few or no staphylococci in the nose. Indeed, it is even possible that staphylococci from the perineum may be able to reach operation sites on the lower abdomen, groins, buttocks, and of course the perineum itself more easily than those coming from the nose. It is thus unwise in practice to concentrate attention only on the nose.

Though the organisms may come from a carrier site on the patient, we still have to solve the problem of how they get to that site, for there seems to be no doubt that it is not the staphylococci the patient brings into the hospital with him but those he picks up after arrival that are important. In this process the nurse who is a carrier may well play a major part.[6] Not only do nurses tend to carry the hospital epidemic strains but they come sufficiently close to a patient to be able to transfer their own organisms to him by contaminated fingers[7] or as a result of dispersal of staphylococci contaminating their skin and clothing.[8] Nevertheless, transfer by air-borne particles from septic wounds is another possibility.

Thus, though the organisms reaching a patient's wound may have come from a carrier site on the patient himself, it is some form of cross-infection that gets them to him. Cross-infection therefore loses none of its importance, but it is a major step forward to learn that it is the patient's nose (or possibly his perineum) and not his wound that first receives them.

A NEW EPIDEMIC OF GONORRHOEA?

Penicillin has been regarded as the best treatment of gonorrhoea for the past fifteen years. So excellent has been its effect in the acute stage of the disease that optimists were forecasting the conquest of this old scourge. The year of highest incidence after the last war was 1946, when no fewer than 47,343 cases of this disease were treated at the venereal disease treatment centres in England and Wales.[1] A remarkable fall in incidence followed, though it seems reasonable to attribute it as much to times of peace and plenty as to the new remedy. But since 1954 the numbers of patients attending the clinics with acute gonorrhoea have risen, and they have continued to rise year by year.[2] In 1954 the total was 17,536, and in 1957 it was 24,381. One cause of this increase has been the movement of people into Great Britain from various colonies and dependencies, but since 1956 it has become clear that some other factor is at work. At that time it was noticed in London[3–5] that a small proportion of men who were treated for acute gonorrhoea with doses of penicillin which had almost always proved adequate failed to respond or, after apparent response, relapsed within a few days. Strains of organisms isolated from these patients were usually found to be relatively resistant to penicillin. Subsequently similar reports were received from various centres in the provinces, and it was also reported that the same problem had been encountered in Japan.[6] In Denmark A. Reyn and colleagues[7] compared strains of gonococci isolated in 1944 and 1957 for sensitivity to penicillin, streptomycin, and tetracycline, and found that some strains isolated in 1957 were relatively insensitive to penicillin. This was in contrast to the experience of 1944, when all were sensitive to penicillin. Sensitivity to streptomycin and tetracycline was about the same in both groups. E. Epstein[8] has recently reported from Korea the results of treating 148 soldiers of the United States Army suffering from acute gonorrhoea with five daily injections, each of 600,000 units of procaine penicillin in aqueous suspension. The treatment failed in 30 cases, in which either the gonococcus did not disappear from the secretions or relapse soon followed the completion of treatment. This failure rate of 20% was contrary to past experience, when failure rates of 1 to 5% had been reported after treatment

[1] Ministry of Health, *Report on the State of the Public Health*, 1957, Part II, p. 280. H.M.S.O., 1958.
[2] *Brit. med. J.*, 1959, **1**, 1235.
[3] King, A., *Lancet*, 1958, **1**, 651.
[4] Cradock-Watson, J. E., Shooter, R. A., and Nicol, C. S., *Brit. med. J.*, 1958, **1**, 1091.
[5] Curtis, F. R., and Wilkinson, A. E., *Brit. J. vener. Dis.*, 1958, **34**, 70.
[6] World Health Organization, *Lancet*, 1958, **1**, 899.
[7] Reyn, A., Korner, B., and Bentzon, M. W., *Brit. J. vener. Dis.*, 1958, **34**, 227.
[8] Epstein, E., *J. Amer. med. Ass.*, 1959, **169**, 1055.
[9] Bernstein, L., *J. gen. Microbiol.*, in press.
[10] Alergant, C. D., *Brit. J. vener. Dis.*, 1958, **34**, 36.

of similar cases with single doses of 300,000 units of the same preparation. It was thought that the probable cause of failure was increased resistance of the gonococcus to penicillin. The author quoted unpublished work by L. Bernstein[9] demonstrating resistance of certain strains of gonococci to penicillin *in vitro*. The organisms were obtained from United States military personnel in Japan who had failed to respond to treatment with penicillin.

The present evidence is that organisms which show resistance are only partially resistant, and clinical cures can be obtained by increasing the dosage of penicillin until blood levels are obtained which are effective against the particular organisms concerned. Judging by past experience with sulphonamides in the treatment of gonorrhoea, the degree and frequency of resistance to penicillin are only too likely to increase. Detailed studies of the gonococcus and its sensitivities are urgently required if a new epidemic of gonorrhoea is to be avoided. The gonococcus is sensitive to antibiotics other than penicillin, but most of them are expensive and no one can foretell how long they will continue to be effective. There is already evidence of resistance to streptomycin, particularly from Liverpool.[10] Investigation into these problems should not be delayed if serious trouble is to be averted.

HYPERPARATHYROIDISM AND PANCREATITIS

Primary hyperparathyroidism may give rise to a variety of symptoms, some of them apparently unconnected with any known action of the parathyroid hormone or hormones. It is not long since peptic ulceration was recognized as an important and relatively common complication of this disorder[1] ; now pancreatitis is seen to be.

Cases of pancreatitis or pancreatic calcification discovered at necropsy in association with primary hyperparathyroidism have been recorded in the literature for many years, and J. B. Gross has recently reviewed this association between the two conditions.[2] He found 14 such cases published between 1923 and 1958 and added one of his own. Many were examples of pancreatic calcification without pancreatitis, but in some pancreatitis was present without detectable calcification. In five of the 15 cases it seemed probable from the histories that the hyperparathyroidism had begun before the pancreatitis and in only one did the reverse appear at all likely ; in nine the time relationship was indeterminate.

This series collected by Gross includes a remarkable family reported by C. E. Jackson,[3] in which there were six cases of hyperparathyroidism. In two of these, recurrent bouts of nausea, vomiting, and abdominal pain were found to be associated with raised serum levels of amylase, and in one of them *x*-ray examination revealed diffuse pancreatic calcification. Gross also refers to two cases reported by O. Cope and his colleagues.[4] The first of these patients developed acute pancreatitis (confirmed at necropsy) during a phase of hyperparathyroidism ; the second was found to be suffering from primary hyperparathyroidism after the serum calcium had been determined during an attack of abdominal pain and shock associated with a very high serum level of amylase. This patient, who had suffered from recurrent pancreatitis for three years, had three further mild attacks after parathyroidectomy, but was subsequently free of symptoms for the three years up to the time of publication.

In the majority of the published cases there was radiological or pathological evidence of pancreatic calcification, and in some the presence of calculi in the ducts could adequately account for the pancreatitis. It is not surprising that pancreatic calcification occurs in hyperparathyroidism, for the concentration of calcium in pancreatic juice normally approximates to that of the diffusible calcium in the plasma.[5] When this is high, it could lead to the precipitation of calcium phosphate in the ducts, particularly in view of the alkalinity of the secretions there.

But there are at least three cases of pancreatitis and hyperparathyroidism in which no evidence of pancreatic calcification was observed radiologically,[3 4 7] and there is one[6] in which post-mortem examination apparently revealed pancreatitis without calcification. It is these cases, and particularly the prompt recovery of one of them after parathyroidectomy,[7] which have suggested that the connexion between the two conditions may be more mysterious than the explanation given above would suggest. Thus Jackson[3] compares the association with the inherited adenomatosis described by P. Wermer[6] as another example of coexisting parathyroid and pancreatic disease. Cope and colleagues[4] mention the possibility that the recurrent hypocalcaemia of severe pancreatitis may lead to secondary hyperparathyroidism and so to parathyroid neoplasia, but clearly do not themselves subscribe to this rather fanciful idea. G. Mixter and his colleagues[7] suggest, perhaps rather obscurely, that " the vascular responses of the involved organs " may prove to be important in the association between the two conditions.

Recurrent pancreatitis is itself a mysterious condition, the diagnosis of which is often uncertain and the pathogenesis undecided. Stasis of secretions in the ducts may play a part in the disorder, but usually no anatomical or mechanical obstruction can be found. The concept of a functional block—though plausible—does not explain all the cases.[8] In primary hyperparathyroidism, however, obstruction of the pancreatic ducts by calcium phosphate calculi has been found in several

[1] Rogers, H. M., *J. Amer. med. Ass.*, 1946, **130**, 22.
[2] Gross, J. B., *Ann. intern. Med.*, 1958, **49**, 796.
[3] Jackson, C. E., ibid., 1958, **49**, 829.
[4] Cope, O., Culver, P. J., Mixter, C. G., and Nardi, G. L., *Ann. Surg.*, 1957, **145**, 857.
[5] Sinclair, I. S. R., *Brit. J. Surg.*, 1956, **44**, 250.
[6] Wermer, P., *Amer. J. Med.*, 1954, **16**, 363.
[7] Mixter, G., Hinton, W. J., and Pfeffer, R. B., *N.Y. St. J. Med.*, 1958, **58**, 3470.
[8] Doubilet, H., and Mulholland, J. H., *J. Amer. med. Ass.*, 1956, **160**, 521.

cases, and it is tempting to infer that this process was responsible for the pancreatitis in the remainder as well. The absence of radiologically visible calcification certainly does not exclude this possibility, and the failure to detect a stone *post mortem* implied in one case report[4] does not entirely rule it out.

On the other hand, it is not inconceivable that some more subtle link exists between the two conditions, the elucidation of which might shed light on them both. In the meantime the association, having been brought to light, will give surgeons another reason to look at the serum level of calcium in cases of acute pancreatitis.

EARLIEST SYMPTOMS OF MEASLES

"It is indeed late in the day to describe something connected with the diagnosis of the exanthemata": so wrote Henry Koplik[1] in 1896 when describing the spots on the buccal mucous membrane that will always be associated with his name. Though measles afflicts ninety-five children out of a hundred in most countries of the world there seems to be some uncertainty about the earliest symptoms of this infection. A pre-eruptive illness lasting for more than a week has been observed in some epidemics, yet several standard textbooks still follow Sydenham's description, in which the rash is said to appear on the fourth or fifth day of illness.

M. W. Partington and J. F. P. Quinton[2] have recently reviewed the notes they recorded on 120 cases of measles seen in two Norwich hospitals with the particular object of assessing the earliest symptoms that could be attributed to the measles virus. Thirty-eight case records were discarded because they lacked precise statements of when the illness began or certain diagnostic criteria, and in 57 of the remaining patients the rash had appeared by the end of the first week. Chief interest in their article centres around the 25 in whom the rash was not seen until the eighth day or later. The symptoms in these patients included fever, lethargy, anorexia, cough, abdominal pain, and vomiting. A transient "pin-head" rash was seen in one child. This pre-eruptive illness persisted in 17 children until the classical rash developed, fourteen days being the longest period, while in the remaining 8 the illness was diphasic, several days of apparently normal health separating the prodromal from the classical symptoms.

The authors are satisfied that their observations fit in with the current theory of the pathogenesis of measles. The measles virus is believed to enter through the respiratory tract, invade the blood-stream for a few days, and then settle in the reticulo-endothelial system to multiply and gather strength for a second invasion, when a more massive viraemia results in the classical and unmistakable symptoms. It is reasonable to assume that the early viraemia may be of sufficient intensity and duration, or the host may be so susceptible, that constitutional symptoms similar to those occurring later will arise during part or the whole of the period of incubation. All the children in this series required admission to hospital, and it would be interesting to know whether a similar proportion of cases seen in general practice show a long prodromal illness. Evidently the early symptoms are those seen in many childhood illnesses and are not diagnostic, but they might occasionally be helpful when it is both desirable and practicable to avoid infecting a young or debilitated baby. The authors deserve congratulation for finding interest in work that some would regard as dull routine.

[1] Koplik, H., *Arch. Pediat.*, 1896, **13**, 918.
[2] Partington, M. W., and Quinton, J. F. P., *Arch. Dis. Childh.*, 1959, **34**, 149.

MUMPS ON AN ISLAND

A population's specific immunity to an infection depends on the degree of previous exposure to the micro-organism causing the disease. When an infectious disease is introduced into a community which has never experienced it in the past, the spread of infection can be studied against a background uncomplicated by specific herd immunity. In the past much has been learned from island epidemics of measles and epidemics of poliomyelitis in "virgin" populations. More recently serological surveys have greatly increased the value of studying epidemics in isolated communities.

In 1957 an epidemic of mumps occurred in "virgin soil" among the Eskimos in St. Lawrence Island, and an interesting account[1] of this has been published. St. Lawrence Island is an island in the Behring Sea and has limited communication with the outside world. So far as could be ascertained there had been no mumps on the island within living memory, although five of the inhabitants had suffered from the disease elsewhere. There were 363 cases of mumps in the epidemic, 65% of the inhabitants of the island being attacked. The population is concentrated largely in two villages. Although equal attack rates were experienced in each village, the duration of the epidemic was twice as long in one as in the other (27 weeks in one and 13 weeks in the other), a difference that was explained by the fact that the epidemic in the latter began with multiple introductions. Orchitis occurred in 38% of the male cases aged 15 years or more, while tenderness and swelling of the breast were found in 31% of the female cases over 15. The frequency of infection was less in pregnant women than in non-pregnant women, a finding which had been previously noted by other American workers.

In view of the absence of past infection from the community the age incidence of the disease is of interest. The attack rate was low (17%) under the age of 1 year, gradually increasing until at the ages 3 and 4 years it had reached a level between 70 and 80%, at which level it remained until the age of 50 years, declining thereafter. In adolescents and adults mumps was more frequent among males than females, although disease confined to the salivary glands was equally common in the two sexes.

Households with between five and eight persons had higher attack rates than smaller households, which was attributed to differences in the intensity of exposure;

[1] Philip, R. N., Reinhard, K. R., and Lackman, D. B., *Amer. J. Hyg.*, 1959, **69**, 91.

but no explanation could be offered for the finding, consistent at all ages, that increase in the size of household above eight persons was associated with a lowering of the attack rate.

The serological survey showed that about two-thirds of those who escaped an attack of mumps developed a positive complement-fixation test during the epidemic. The infection rate was thus much higher than was indicated by the incidence of disease. It is interesting to note that inapparent infections were least common in children of school age and became more frequent as age advanced.

GEOGRAPHY OF PEPTIC ULCER

One of the outstanding features of disease is its geographical variation. Often we understand the reason for regional differences. For example, we know that malaria occurs only where suitable anopheline mosquitoes can live because they are the vector of the malaria parasite, though it is not long in terms of human history since fantastic theories were advanced to explain its occurrence in one place but not in another. Some of the serious diseases of to-day show regional differences without our understanding why. Such a one is chronic peptic ulcer, which incidentally seems to be far more common in Western society than it was fifty years ago. Its incidence in Africa, and some of the difficulties in determining the true incidence, have recently been discussed in this journal.[1–3]

A comparative study of gastro-duodenal ulcer and cancer in different countries has now been made by W. Nimeh.[4] His study takes the form of the collected answers given to a standard questionary by 82 medical authorities on the subject from 33 countries, covering all colours of the skin and every type of race and civilization from Aztec to Soviet Russian, from Bantu to Yaqui. Though much of the study contains familiar material, it is nevertheless refreshing to ponder the experience and opinions of physicians working outside the ambit of Western society. In Alaska there were no reported deaths from gastric or duodenal ulcer among the Eskimos during the period 1945–7, according to Dr. C. E. Albrecht, the Commissioner of Health, though he states that such deaths may have occurred without being reported as such. In Arabia a considerable number of the native inhabitants were admitted to the hospitals of the Arabian–American Oil Company with gastric or duodenal ulcer or one of their complications. F. G. Scovel writes, "Peptic ulcer in China seems to be common among the active middle class who are assuming responsibilities of business or public office; especially if they are prone to be nervous," while C. Wang remarks that duodenal ulcer appears to be about three times as common as gastric ulcer in China. In the subcontinent of India peptic ulcer appears to be uncommon in West Pakistan, more common in East Pakistan, and very common in South India. In South Africa the Bantus seem singularly free from chronic peptic ulcer. Thus it is recorded that a hospital pathologist in Johannesburg who has carried out about 700 post-mortem examinations a year for 15 years on Bantus has seen only three cases of duodenal ulcer and about five of gastric ulcer.

While many of the data given in this study lack precision, some of the geographical and racial differences are too startling to be mere artifacts. When future work has solved the riddle of chronic peptic ulcer, we may find that the facile explanation sometimes given to-day that it is a disease of civilization due to mental stress will seem as remote from the truth as the view that malaria is caused by foul vapours ascending from the swamps.

[1] *Brit. med. J.*, 1959, **1**, 1462.
[2] Baldachin, B. J., and Palmer, P. E. S., ibid., 1959, **2**, 304.
[3] Konstam, P., ibid., 1959, **2**, 304.
[4] Nimeh, W., *Symposium on Gastroduodenal Ulcer and Cancer*. Volumes II and III. Publications de l'Université Libanaise, Beyrouth, 1959.

A NEW GENETIC SYNDROME

As knowledge of human genetics becomes more exact it is found that many similar syndromes can be caused by different gene mutations. Usually the genetically distinct syndromes are only similar clinically, and not identical. Two recent examples are the differentiation of Christmas disease from classical haemophilia,[1] and the distinction between the autosomal recessive and the sex-linked recessive forms of pseudo-hypertrophic muscular dystrophy.[2]

A condition whose precise genetic aetiology is still in dispute (one, or several, autosomal recessive genes?) is the syndrome of obesity, hypogenitalism, polydactyly, retinal degeneration, and (usually slight) mental retardation. This syndrome, apart from polydactyly, was described nearly 100 years ago by Laurence and Moon,[3] and polydactyly was added by Bardet[4] and Biedl.[5] The syndrome is apt to vary considerably, and it is not easy to decide, while the exact nature of the abnormality is still unknown, whether the variation between families is more than that between affected members of the same family.

This year three patients in the same family, two men and a woman, have been reported from Sweden[6] with a syndrome which, though similar, is almost certainly distinct from the Laurence–Moon–Bardet–Biedl syndrome. The symptoms in these patients were retinal degeneration, obesity, nerve deafness, and diabetes mellitus. In one patient the evidence for the diabetes mellitus was only an abnormal sugar-tolerance curve. The grounds for regarding the syndrome as distinct are: the absence of mental deficiency, polydactyly, and hypogenitalism (though tubular sclerosis was found on testicular biopsy of one patient); the presence of nerve deafness and diabetes mellitus; and the fact that the retinal defect caused nystagmus and early loss of central vision, in contrast to loss of peripheral vision. The combination of signs appears to be unique, and the similarity of the manifestations in all three affected members of the same family strongly suggests that it is a distinct clinical entity. The family history of the patients indicates autosomal recessive inheritance.

[1] Biggs, R., *et al.*, *Brit. med. J.*, 1952, **2**, 1378.
[2] Bly h, H., and Pugh, R. J., *Ann. Hum. Genet.*, 1959, **23**, 127.
[3] Laurence, J. Z., and Moon, R. C., *Ophthal. Rev.*, 1866, **2**, 32.
[4] Bardet, G., Faculté de Médecine de Paris, 1920, These 470.
[5] Biedl, A., *Dtsch. med. Wschr.*, 1922, **48**, 1630.
[6] Alström, C. H., Hallgren, B., Nilsson, L. B., and Asander, H., *Acta psychiat. scand.*, 1959, **34**, suppl. 129.

CLINICAL BIOCHEMISTS AND CLINICAL PATHOLOGISTS

JOINT MEETING IN LONDON

[FROM SPECIAL CORRESPONDENTS]

On October 3 the Association of Clinical Biochemists and the Association of Clinical Pathologists held a joint meeting at the Royal College of Surgeons. In the morning there were two symposia—on "Thyroid Antibodies" and "Enzymes, Esterases, and Cholinesterase"—which are reported below; in the afternoon there were short papers.

Thyroid Antibodies

The subject of thyroid auto-antibodies in relation to thyroid disease occupied the first half of the morning session. Dr. I. M. ROITT and Dr. DEBORAH DONIACH (Middlesex Hospital) described the principal auto-antigens which give rise to the antibodies found in such profusion in the sera of patients with Hashimoto's thyroiditis—viz., the protein thyroglobulin present in the acinar colloid as a precursor of circulating thyroid hormone and an intracellular constituent present in normal glands but particularly abundant in the thyrotoxic thyroid. Antibodies to thyroglobulin could be demonstrated in 90% of Hashimoto patients by precipitation in gel or by tanned-cell agglutination techniques, they said. The latter test had been simplified for routine clinical use by the development of a stable preparation of formolized thyroglobulin-coated sheep red cells. The intracellular antigen was localized to the microsome fraction of thyroid epithelial cells and gave rise to complement-fixing antibodies which are present in over 90% of Hashimoto patients. These two immune systems were completely independent and some patients had only one or the other of the antibodies. Their separate nature could be clearly demonstrated by the Coons fluorescent-antibody technique. Thyroglobulin antibodies stained the colloid in alcohol-fixed sections of thyroid, whereas complement-fixing antibodies stained the cytoplasm of the acinar cells in unfixed sections.

Evidence had also been obtained that certain Hashimoto patients who have raised sero-flocculation tests but give negative results by the tanned red-cell and complement-fixation tests have antibodies directed against a colloid constituent other than thyroglobulin, demonstrable by the Coons technique. Hashimoto sera had been shown to be cytotoxic to trypsinized human thyroid cells in tissue culture. The cytotoxic factor was inactivated by heating to 56° C. for 30 minutes, and killed only cells cultured for up to 36 hours. In the majority of patients with thyroiditis auto-immune phenomena were confined to the thyroid gland, but about 10–15% of cases showed a more widespread disturbance of immunological reactions, and either gave positive complement-fixation with saline extracts of other human organs or the nuclear fluorescent-staining reaction associated with lupus erythematosus. Very occasionally patients had both thyroiditis and evidence of systemic lupus with positive L.E. cells.

With regard to the aetiology of Hashimoto's thyroiditis, the presence of the circulating antibodies thus far characterized seemed inadequate to account for the progression of the lymphoid lesions; however, the role and nature of the agent cytotoxic to tissue cultures had yet to be elucidated. In the experimental auto-allergic diseases the view was current that hypersensitivity of the delayed type is responsible for the histological damage, but so far the evidence in human chronic thyroiditis was inconclusive. It was of interest in this connexion that the lymphocytes of the Hashimoto gland exhibit unusual behaviour in tissue culture and appear to be attracted to the thyroid cells and even seem to enter their cytoplasm.

Diagnostic Significance

Dr. J. R. ANDERSON, Dr. R. B. GOUDIE, and Dr. KATHLEEN GRAY (Western Infirmary, Glasgow) considered the incidence and diagnostic significance of the serum auto-antibodies in thyroid diseases. Complement-fixing antibodies, reacting with saline extracts of thyrotoxic thyroid, were found in 90% of cases of Hashimoto's disease, over 50% of cases of thyrotoxicosis and primary myxoedema, and in 7% of hospital patients with no clinical evidence of thyroid disease. In the latter group a positive complement-fixation test was associated with mild focal thyroiditis; the presence of areas of Askanazy-cell change and round-cell infiltration in the thyroids of these patients was considered to be the result of auto-immunization. The common occurrence of complement-fixing antibodies in various thyroid diseases made the complement-fixation test of little diagnostic value although it provided an indication of lymphadenoid change. The precipitin test for circulating thyroglobulin, however, was positive only in patients with clinically significant thyroiditis (i.e., Hashimoto's disease), primary myxoedema (which is considered as a variant of the same underlying disease process), or severe focal thyroiditis complicating thyrotoxicosis or carcinoma of the thyroid. Where the precipitin test was positive, surgical treatment should be undertaken only if there was strong suspicion of carcinoma or if medical treatment failed. There was a high probability that thyrotoxic patients giving a positive precipitin test would develop post-operative myxoedema.

Cause or Result of Damage

The discussion was opened by Dr. W. R. TROTTER (University College Hospital, London), who underlined the outstanding problem of whether the auto-antibodies are the cause or the result of the damage to the thyroid in Hashimoto's disease and primary myxoedema. There were two alternative possibilities, he said. The first was that a relatively trivial damage to the thyroid released antigenic material which stimulated the production of antibodies. These antibodies might react on the thyroid to cause further tissue damage, further release of antigens, and further production of antibodies in a chain reaction which could progress to ultimate destruction of the gland. The second hypothesis supposed that the unknown agent (invoked in the first hypothesis merely as an initiating factor) was responsible for *all* the tissue damage. As a secondary consequence of this damage, antigenic material was released and stimulated antibody production, but these antibodies did not in themselves cause any further lesion. On this view the antibodies only provided an indication of thyroid damage. The first hypothesis was supported by the rough correlation between the level of serum antibody and the apparent activity of the destructive process in the gland, and by the experiments of Witebsky and Rose, who had demonstrated that injection of rabbits with extracts of rabbit thyroid could lead to antibody production and lesions in the thyroid. However, this hypothesis failed to provide a satisfactory explanation of cases with more localized, non-progressive lymphadenoid change where there was demonstrable damage to thyroid tissue coexisting with circulating antibodies. The cytotoxic effect of Hashimoto sera on thyroid cells in tissue culture was compatible with either hypothesis. The cytotoxic factor was not identical with the thyroid antibodies studied by the routine precipitation and complement-fixation tests, and it would clearly be of importance to determine whether or not it was an antibody.

In clinical practice, Dr. Trotter found the presence of antibodies helpful in the diagnosis of hypothyroidism in doubtful cases, and in general considered that the serological tests were of value, although low titres of antibodies in thyrotoxicosis probably had no clinical significance. He found no correlation between complement-

fixation titres and the incidence of myxoedema following treatment of thyrotoxic patients with radioactive iodine.

Cholinesterase

Dr. W. N. Aldridge (M.R.C. Toxicology Research Unit, Carshalton) spoke on the estimation of cholinesterases. There were two types of human cholinesterase. One was found primarily in the nervous tissue and in the red cells and was referred to as the "true" cholinesterase; the other was associated particularly with the plasma and the pancreas and had been named "pseudocholinesterase." This nomenclature implied that the first, the true cholinesterase, was in fact the enzyme which hydrolysed acetylcholine in nervous transmission. The physiological role of the second enzyme was not clear. The estimation of the two enzymes required their differentiation from each other and of both of them from the human aliesterases and lipases.

It had always been known that pseudocholinesterase could hydrolyse non-choline esters. It was perhaps less well appreciated that the true cholinesterase could attack a variety of acetic esters other than acetylcholine. In that sense the cholinesterases were less specific than the aliesterases and lipases. By using in the determination of cholinesterase activity choline esters only as substrates one made sure that there was no interference by non-specific hydrolysis by the other human esterases. If both cholinesterases were present it was usual to distinguish between them by using different substrates. The true cholinesterase was less and pseudocholinesterase more active with the higher homologues of acetylcholine. Nevertheless true cholinesterase could hydrolyse propionic choline about one-third as fast as pseudocholinesterase, and, although the pseudocholinesterase was twice as active with n-butyrylcholine as with acetylcholine, the true cholinesterase had some small but definite effect on this compound. It was undesirable therefore to use these esters for the estimation of pseudocholinesterase when the true cholinesterase was also present. The most specific and suitable substrate for the determination of true cholinesterase was acetyl-β-methylcholine, and for pseudocholinesterase benzoylcholine. Nearly all methods measured the amount of acid produced on ester hydrolysis. In the Warburg method bicarbonate buffer was used; the acid liberated carbon dioxide which could be measured manometrically. This technique gave proper rate measurements and was unaffected by the protein content and the colour of the enzyme preparations. The amount of acid could also be measured by using a *p*H-meter or an indicator. One could either determine how much alkali had to be added to keep the *p*H constant or one could determine how much acid was produced. In some of these techniques no account was taken of the influence of the *p*H change on the activity of the enzyme. There was a useful field technique in which blood was added to bromophenol-blue indicator and the time was measured in which the colour of the indicator was changed. There was one method in which β-carbonaphthoxycholine iodide was added to plasma. This substance was claimed to be a specific substrate of pseudocholinesterase. After removal of the choline this compound gave a colour reaction.

Dr. J. H. Wilkinson (Westminster Hospital, London) had used β-carbonaphthoxycholine iodide for the determination of pseudocholinesterase, but had found it gave too high a blank value to be of practical use.

Clinical Applications

Professor R. H. S. Thompson (Guy's Hospital, London) discussed the clinical applications of cholinesterase estimations. These referred mostly to pseudocholinesterase. The plasma pseudocholinesterase was reduced in liver damage and malnutrition. The relation between the plasma pseudocholinesterase and liver function had been demonstrated by measuring the rate of regeneration of this enzyme after it had been destroyed by administration of the organophosphate poison D.F.P. There was a much lower rate of regeneration in liver disease.

The response of patients to the muscle relaxant succinylcholine was related to the plasma pseudocholinesterase level. This compound was destroyed by pseudocholinesterase, hence it was short-acting. If the enzyme level was low, prolonged apnoea was encountered. In some patients with prolonged apnoea liver disease could not be blamed as the cause of their low pseudocholinesterase level, and it was found that they were homozygous for a genetic defect. A number of families with a familial low pseudocholinesterase level had now been described, and it had been claimed that the abnormality was not one of pseudocholinesterase level but that the enzyme itself was different in these families. Pseudocholinesterase was also low in organophosphorous poisoning. Anticholinesterases used for pest control in agriculture could cause the condition. The measurement of cholinesterase was useful for discovering slight poisoning which had not yet produced clinical symptoms. The individual enzyme level was constant, but in the general population the normal range was wide. Some firms established a baseline in their employees so that subsequent changes could be detected, even if they occurred within the normal range.

Plasma pseudocholinesterase was raised in the nephrotic syndrome and in about half of patients with thyrotoxicosis. It had at one time been thought that the enzyme level was raised in diabetes. However, when diabetic patients were subdivided in obese and thin subjects it was found that the high pseudocholinesterase was associated with obesity, and that in fact pseudocholinesterase tended to be high in obesity generally. In cholinergic urticaria true and pseudocholinesterase levels were normal in the blood, but the pseudocholinesterase level was low in the affected areas of the skin. This agreed with previous observations which had established that wealing of the skin occurred in this condition although the amount of acetylcholine released at the nerve endings was normal.

There were no changes in the enzyme levels of cells and plasma in myasthenia gravis, but it had been stated that in 7 patients the true cholinesterase level had been found to be raised in the C.S.F. Professor Thompson had himself examined so far three patients for this phenomenon, but had found in them no abnormality. Reticulocytes contained more true cholinesterase than other red cells, and red-cell cholinesterase rose in reticulocytosis. This rise could persist even when the reticulocytosis had subsided. It had been suggested that measurement of true cholinesterase in the blood might be a sensitive means of measuring reticulocyte response.

Organophosphate Poisoning

Dr. D. R. Davies (Chemical Defence Establishment, Porton) described the chemotherapy of poisoning with organophosphate anticholinesterases. These compounds caused a lethal accumulation of acetylcholine because they inactivated cholinesterase by phosphorylating the enzyme's active centre. For many years atropine had been the only effective antidote. Unfortunately atropine had undesirable physiological effects of its own, and, though it counteracted the muscarinic effects of acetylcholine, it could only partially reverse those on the C.N.S., and not at all those of the nicotinic type. An antidote against the phosphorylating poisons should either divert the poison from the enzyme by competing with it for phosphorylation or it should restore the phosphorylated enzyme by dephosphorylation. In either case it would have to possess a high intrinsic reactivity with organophosphoryl compounds.

In recent years derivatives of hydroxyiminomethylpyridinium had been found to show this property both *in vivo* and *in vitro*. P.A.M. (pyridine-2-aldoxime methiodide) had been introduced. It could reverse neuromuscular block due to organophosphates, and in less serious cases of poisoning might obviate the need for atropine as well. The corresponding methane-sulphonate salt P2S was more soluble and had also been widely used. There were in Japan about 1,000 cases of parathion poisoning every year.

Recently 39 patients had been treated with P.A.M. In all but five of the most severe cases 1 g. of P.A.M. had helped in their recovery. In four of these five 2 g. of P.A.M. had succeeded in securing recovery, and only one patient died. This was a man who had taken an excessive dose to commit suicide. Some of the anticholinesterases continued to be absorbed or to be converted into active inhibitors for some time after administration of the poison. It was necessary to continue giving P.A.M. or P2S for some time to reap the full benefit of the new treatment. As much as 5–10 g. of these compounds had been given by mouth to man without ill effect and 2 g. had been administered by intravenous infusion.

Pseudocholinesterase in Liver Surgery

Mr. A. H. HUNT and Dr. H. LEHMANN (St. Bartholomew's Hospital, London) had compared the value of serum pseudocholinesterase estimation with other laboratory investigations in patients with liver disease undergoing porta-caval and lieno-renal venous shunt operations. The pseudocholinesterase values fluctuated from case to case, but values below 35 Warburg units indicated that the prognosis was not good, though they should not prohibit the operation. In individual patients alterations in pseudocholinesterase level gave a more immediate estimate of the patient's day-to-day or week-to-week response than any other test. If on the other hand the serum albumin level was below 3.2 g./100 ml. the operation should be postponed and a course of medical treatment should be instituted, the success of which should be judged by a rise of the serum albumin level above this critical level. As Professor Thompson had pointed out, for mild organophosphate poisoning, so in mild cirrhosis a single test could fail to indicate cirrhosis because of the wide range of normal values, but when a baseline existed for any patient alterations within the normal range could be used for purposes of diagnosis. An interesting observation was that pseudocholinesterase was raised in alcoholism.

ATOMIC WAR

The appalling numbers of casualties that might occur in a war fought with nuclear weapons, and the still mysterious nature of the injuries they might suffer, provided much material for discussion at the Army Medical Services conference held on October 1 at the R.A.M. College, Millbank, London. Sir ALEXANDER DRUMMOND, Director-General of the Army Medical Services, welcomed the speakers.

Neutrons in the Gut

Lieutenant-Colonel J. A. H. BROWN said that a large nuclear weapon of perhaps 20 megatons exploded over the College would have immediately lethal effects as far as Penzance. From such weapons gamma radiations were the main danger, but there were small nuclear weapons from which neutrons were emitted and caused damage. Animal experiments indicated that neutrons acted principally on the gut, not on the bone-marrow like gamma radiations. Death was from intestinal failure. These small weapons might also cause failure of the nervous system.

Dr. J. F. LOUTIT, of Harwell, dispelled any hope of finding in the near future a simple pill to prevent the effects of radiation. Prevention was better than cure, he said. The well-tried methods used in industry showed that the best protectives were distance from the nuclear discharge, and physical barriers. Hydrogen in some form gave the best protection against neutrons. Concrete was a dual-purpose protective, being a barrier to neutrons as well as gamma rays. Apart from damage to the cell nucleus that atomic radiations can cause, Dr. Loutit referred to the damage by oxygenation. This was due to the OH radicles liberated from ionized water in the body tissues.

Professor J. R. SQUIRE, of Birmingham, discussed how the harmful effects of radiation could be mitigated. A dose of potassium iodide might prevent concentration of radioactive iodine in the thyroid. To reduce the oxygenation by OH radicles a possible treatment immediately would be to lower cell metabolism by giving the patient complete rest, perhaps with heavy doses of phenobarbitone, and in special circumstances applying local cooling (e.g., to an irradiated limb). Pyridoxine or chlorpromazine might be given to stop vomiting, and salicylates might cut down capillary permeability. Cortisone or its derivatives might also help. From the beginning the control of infection was a major problem. Penicillin should be tried before the other antibiotics; neomycin was useful for gut sterilization; gamma globulin was worth giving. Barrier nursing should be done when practicable. Blood should be given only when there was a definite indication for it. Platelet transfusions might be needed.

Alone and Palely Loitering

In any war soldiers are apt to find themselves suddenly cut off from their units and to react with some dismay at this severance. A good morale and the cultivation of it were discussed in a section entitled "Isolation—The Will to Live." It was the occasion for some manly reminiscences about polar exploration and for a very moving account by one of the ladies present, Lieutenant-Colonel E. M. TURNER, Q.A.R.A.N.C., of her solitary voyage on a raft off Singapore during the last war.

Dr. E. A. BENNET thought a better title would be "Isolation—and Opportunity for Initiative." He said that initiative was something that had to be instilled into many soldiers in order to give them the will to live. Dr. G. W. B. JAMES agreed that soldiers differed greatly in this respect, and suggested that the R.A.M.C. should study the "embryology of character" to find out more about the responses to be expected from soldiers of different psychological type and how they might be modified by training.

Several speakers referred to the encouragement that could come from firm religious beliefs, though one added that they were no substitute for adequate ammunition.

Quick Anaesthesia

One of the problems posed by a nuclear attack might be to provide anaesthesia quickly for the performance of short life-saving operations on a large number of casualties without many skilled anaesthetists. Colonel K. F. STEPHENS demonstrated an apparatus for administering cyclopropane, nitrogen, and oxygen for up to about 10 or even 20 minutes. It had been developed from one designed by Dr. J. G. BOURNE, of London, who also spoke. The advantages claimed were that the low blood solubility and low toxicity of cyclopropane made it relatively safe, the mixture was non-explosive (though cyclopropane is inflammable), and the use of the apparatus could be quickly taught to nurses and orderlies.

The scheme was criticized by some of the other anaesthetists present, and also later by a surgeon, who said he did not know of an operation likely in these circumstances that he could do in 10 minutes.

The perennial subjects of traumatic surgery were also discussed at various sessions. They included the treatment of burns, for which Major A. V. FORAGE advocated polythene covering as a first-aid measure. He suggested cutting away burnt clothing and then covering the body or limbs individually with polythene sheets and tubes. They would prevent loss of fluid through the burnt area by maintaining 100% humidity in the surrounding atmosphere. Succeeding speakers dwelt on the dangers of sepsis and sogginess, and did not altogether agree with the idea.

NEW ACADEMIC YEAR

CHARING CROSS HOSPITAL

Delivering the inaugural address to the Charing Cross Hospital Medical School on October 1 at the Royal College of Physicians, Lord Justice DENNING took as his subject the relationship between medicine, morals, and the law.

Medicine, Morals, and the Law

In this scientific age, he said, it was possible to circumnavigate the globe at speeds greater than sound, to put satellites into orbit round the earth, and to send rockets to the moon, yet crime had increased at a higher rate than ever before. It seemed that some people had failed to realize the importance of the age-old questions: "What is truth?" "What is justice?" "What is right?" "What is wrong?" "What is good?" "What is evil?" To these, the scientific age gave no answer.

Medicine, which was in the van of scientific development, was daily faced with moral questions, and in particular the simple duty of telling the truth. One of the leaders of the medical profession had recently been reported as saying that it was not right to tell a man the truth when he was suffering from cancer. There was something wrong, Lord Denning declared, with a morality which proclaimed that it was right to tell a lie even for a good cause. There was no absolute rule, but he suggested as a general principle that the duty of the doctor was first and foremost to tell the truth. If, as a matter of expediency, he failed to do so, patients might come to feel that they could not rely on a doctor's word and their confidence would be destroyed. There were many cases involving moral issues which doctors had to decide for themselves. As examples, he mentioned sterilization at a patient's own request, abortion (which in this country was legal only in order to save the mother's life or health, but in over-populated countries such as Japan was accepted), and the problem of artificial insemination which had recently arisen. Great moral issues were involved, and there could be no morality without religion.

Turning to medicine and the law, Lord Denning pointed out that in cases of personal injuries the medical man's reports were vital in order to assess the damages. Doctors also conducted tests when a person was charged with driving under the influence of drink, and in the criminal courts the psychiatrist tried to assess the measure of responsibility of the criminal. Lord Denning felt that, with the extension of psychiatry and psychology, too much blame was placed on parents or other circumstances. "We need a much more bracing philosophy, whereby each individual is accountable for his own actions and should not be allowed to avoid his responsibility except under judgment of the Court," he said.

The sterilization or elimination of social misfits or the mentally deranged to save expense to the community were expedients which could not be reconciled with the doctor's duty to care for the sanctity of human life, cure the sick, and relieve suffering. All those entering the great scientific field of medicine should remember that they would have to face other problems, moral and religious, if they were to do their duty by the profession, the country, and the world at large.

ST. GEORGE'S HOSPITAL

Dr. A. E. CLARK-KENNEDY, a former dean of the London Hospital Medical College, took as his theme for the inaugural address to the St. George's Hospital Medical School on October 2, "The Power of Medicine."

The Power of Medicine

"There are two sorts of intellect," George Gissing had written, "an intellect of the brain and an intellect of the heart." Of these, Dr. Clark-Kennedy considered that intellect of the heart was the more important, and in

(*Continued at foot of next column*)

To day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Tyrimide (Smith, Kline, and French).—This is 2:2-diphenyl-4-diisopropylamino-butyramide methyliodide, another in the ever-growing series of parasympatholytic drugs which have a depressant effect on gastro-intestinal motility and secretion. It is dispensed in 5-mg. tablets.

Experiments on human subjects, in which an oral dose of 30 mg. was used, have shown that the drug causes appreciable reduction in gastric secretion for as long as 10 to 12 hours, and radiological investigations have suggested that a similar oral dose depresses gastro-intestinal motility.

Tyrimide is intended for the treatment of the pain of peptic ulceration, and its prolonged action is of particular value for patients who suffer from pain during the night. Good symptomatic results have been reported with doses of 5 to 10 mg. twice daily, but larger doses may be given. Anticholinergic drugs have been tried in a variety of other gastro-intestinal complaints, including functional disorders of small and large bowel, regional enteritis, and ulcerative colitis, but the results have seldom been encouraging, and tyrimide has yet to be proved superior to other parasympatholytic agents in this respect.

Side-effects.—The usual unwanted anticholinergic side-effects may occur with tyrimide. They include constipation, dryness of the mouth, and blurring of vision. It should not be prescribed for patients who suffer from pyloric obstruction, glaucoma, or prostatic hypertrophy, since the obstructive symptoms in all these conditions are exaggerated by parasympatholytic effects.

N.H.S. Basic Price.—50 tabs. for 14s. 5½d.

(*Continued from preceding column*)

choosing between a batch of students of equal intelligence of brain he preferred the one who would exercise right judgment, realizing that many problems of medical practice were of a moral nature and that human rather than scientific considerations often had to be taken into account in determining medical actions.

When he first took up medicine, there were only six diseases which could be treated medically: diphtheria, tetanus, spirochaetal disease, malaria, amoebic dysentery, and myxoedema. There was no specific treatment for diabetes, pernicious anaemia, Addison's disease, pneumonia, typhoid, or septic infection. The first world war had been fought without any treatment for sepsis, and penicillin had only been introduced on a large scale in time for the invasion of Normandy. To-day birth could be controlled and A.I.D. advocated, and, even if the span of human existence had not been prolonged, a far greater proportion of the human population lived out the full span. Increasing power was being obtained not only over the human body but also over the human mind, and this power could lead to dangerous problems if not exercised aright. Whereas in the old days the problem had been whether a doctor could keep his patient alive, the problem that faced him now was whether he should avail himself of the methods of modern medical science to prolong life, or whether it would not be better to let nature take its course and allow the patient to depart this life in peace. Medicine did not deal with inanimate objects but with individual human beings, and it was impossible to practise medicine without realizing that medical and moral problems collided over and over again.

Dr. Clark-Kennedy said his only fear was that, as a result of increasing power over the body and increasing technical skills, over-emphasis in medical education would be placed on intellect of brain at the expense of intellect of heart. He remained convinced that right understanding was essential if modern medicine was to fulfil its task of reducing human suffering.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Medical Evidence

Sir,—The Podola case must raise an old question in the minds of many doctors: is our present system of medical evidence really the best way of presenting our opinions to a lay jury?

Reading the newspaper reports leaves one with the impression that the results of cross-examination are not always to clarify the minds of the jurors. (Nor, though this is of course less important, do they always enhance the dignity of the profession.) Here were many doctors of undoubted integrity and experience; all, presumably, went into court with clear ideas of what they felt; most of them had examined the case, some for several hours, on different occasions; some had even had a training in the specialty alleged to be concerned. Yet the evidence was very contradictory, and one wonders how many of them came out of court satisfied that they had really got their opinion across to the jury.

It is easy to understand how this can happen in the tense atmosphere of a murder trial and its publicity, and the relentlessness of a cross-examination, which must sometimes stress one point at the expense of the balance of the total picture, on which a diagnosis rests. I suspect that few people in other walks of life would regard the surroundings as best likely to an objective presentation of ideas.

Our naturally patriotic view is that British justice is the best in the world, but this should not prevent us from paying it the compliment of a critical look, and asking whether the system of cross-examination, which may well be the best way of eliciting matters of fact, is also the best way of obtaining an expert's real opinion. I have no direct experience, but I believe that in some other countries the expert witness, singly or as one of a panel, is examined by the judge. I think many doctors would prefer this. And since, as the judge in the case reminded us, Crown counsel is not there to win a case but to elicit the truth, and since Defence counsel has surely no lower aim, the legal profession would presumably welcome any measure which in fact improved the witness's ability to present his opinion clearly.

Is it the moment to suggest that the B.M.A. select a committee to discuss this with the legal profession?—I am, etc.,

University College Hospital, London, W.C.1. R. F. Tredgold.

German Medicine Abroad

Sir,—I have recently completed a short-term appointment in South-east Asia, and on my return stopped at Istanbul and Athens. The number of business men, cars, and strident tourists from West Germany was most impressive. Apart from displacing Britain in the economic field, what also disturbs me is to see the way British medicine has taken second place to German, particularly in Turkey and Greece. In all the hospitals I visited I found specialists who had had their post-graduate training in Germany, and also equipment, pharmaceuticals, textbooks, and medical films from that country; in the university clinics in Istanbul and Athens I met resident German students on exchange.

Postgraduates have no difficulty in being accommodated in German universities and hospitals. There are hundreds of Turkish doctors and technical students in Germany, whereas in the United Kingdom there are only five postgraduates (medical and non-medical) sponsored by the British Council. The leading medical and scientific bookshop in Istanbul had two British textbooks; all the other textbooks were American or German. When I asked the manager about this he replied that these countries allowed him to pay in Turkish currency. An English teacher told me that the German high school gave the best education and that the German hospital was the most popular.

Such is the decline of British influence in a part of the world where once we had many friends. But we still have admirers who would like to know more about British medicine, to study in this country, and, perhaps more important for our national survival, to buy our goods.

Often one has heard the familiar excuses of being a smaller country with a smaller population and fewer universities than West Germany. These are not the facts. West Germany has an area of 95,700 square miles compared with our 93,000. Her population is about the same, around the fifty million mark. She has 15 universities in the fullest sense and 3 technological universities. Admittedly, we try to give priority to students from the Commonwealth, but it should be possible to set aside one or two token places in our universities and teaching hospitals for students outside the Commonwealth. Perhaps in this way and by revivifying our information services we may be able to maintain our prestige and compete with Germany.

History repeats itself, but we do not learn from it. The Allies have rehabilitated West Germany after the recent war as they did after the first, and, with the rapid resurgence of that country in the economic and cultural field, we are being left well behind.—I am, etc.,

Obstetric Hospital, University College Hospital, London, W.C.1. W. C. W. Nixon.

Research and the Clinician

Sir,—In Professor R. F. Farquharson's article on "The Value of Participation in Research in the Continuing Education of the Practising Doctor" (*Journal*, September 5, p. 334) he writes of the dangers of distraction and dissipation of effort in the research worker. An example he uses to illustrate this point is ill-chosen. He says: "To devote all his spare time to an extrinsic subject, such, for instance, as the study of tissue culture, actually tends to reduce a practitioner's interest in his patients and their disorders."

Tissue culture is a method of investigation, and, appropriately applied, is no more an extrinsic subject than bacteriology, virology, electronics and radiation physics, biochemistry, and many other skills and sciences that the educated doctor should know something about. If a clinical practitioner interested, for example, in the biology of tumours believes that a study of tumours in culture might shed some light on his problem, it is hard to see why his special aptitude in that chosen method should reduce his interest in the disorder he is investigating. The study of tissue culture is not an

isolated, extrinsic subject, an end in itself, but a technique that has application to a wide range of problems.—I am, etc.,

Department of Surgery,
The Banting Institute,
University of Toronto.

T. P. Morley.

New Sulphonamides

Sir,—In your leading article on new sulphonamides (*Journal*, September 19, p. 482), reference was made to sulphaphenazole ("orisulf," Ciba). Earlier this year I and some of my colleagues were given an opportunity to try out this new long-acting sulphonamide under general-practice conditions. The advantages claimed for this compound are length of action and freedom from any side-effects. Although there may be a number of possible indications for use of a sulphonamide as an alternative to an antibiotic, it was felt that at this stage it was better to limit the trial to those conditions in which there is an absolute indication for the use of a sulphonamide. The trial was therefore confined to cases of genito-urinary infections, acute conditions being preferred. It was felt that in chronic infections of this type many other factors such as mixed infections and structural damage play a part, and it is not always easy to evaluate the part played by an antibacterial drug.

In general practice, acute urinary infections are not uncommon. The usual procedure is to treat these without, in the majority of cases, sending urine specimens to the laboratory for accurate determination of the infecting organisms and sensitivities to antibacterial drugs. The diagnosis is made on the typical history and symptoms and confirmed by examination of the urine. Albuminuria is not invariably present, but the characteristic fish-like odour may be apparent in the urine. In the absence of any positive finding in the urine, the diagnosis is still made on the typical signs and symptoms. Usually a short course of a sulphonamide over a period of 5–7 days is sufficient to clear up these cases, and, if this does not occur, then further investigations in hospital may be required. The rapid resolution of the condition with specific treatment is further confirmatory evidence of the accuracy of the diagnosis. For instance, there can be little doubt about the diagnosis in a young person attending the surgery complaining of shivering, temperature, frequency of micturition, and pain at the end of micturition. Very often haematuria is also present at the onset of the infection, and the rapid resolution of all these symptoms, without recurrence, confirms the diagnosis. In some cases repeated attacks occur, but these are not chronic cases. For instance, "honeymoon" cystitis is common in newly married couples, and repeated attacks may recur with intervals of a month or two in between. These are classed as acute attacks, since each episode is a separate infection and treatment and resolution are similar to an isolated acute attack.

In all, 22 cases of acute genito-urinary infection were treated, three cases of chronic infection, and three cases of acute bronchitis. The trial in the few cases of acute bronchitis was of an exploratory nature, since it was felt that this might be another condition in which a sulphonamide might be useful as an alternative to antibiotics. Of the acute genito-urinary infections 14 cleared up completely and four resolved partially. Of the chronic genito-urinary infections, one cleared up completely and two resolved partially, whilst in the cases of acute bronchitis two cleared up completely and one resolved partially. In four of the acute genito-urinary infections there was no response to the treatment at all. In dealing with these infections the only real criterion of a successful drug is complete resolution, so that these results showed a 64% cure rate with sulphaphenazole. If the failures are now analysed, it is seen that in a few cases there was a valid reason for the failure. These were as follows: proved resistant organisms (1), chronic infection (2), underlying abnormalities (1). In the remaining cases there was subsequent resolution to antibiotics, so that it is presumed that the organisms were resistant to the sulphonamides in the first instance. The dosage used was 1 g. (two tablets) twice daily for adults, with proportionate reduction in dosage for children. The drug was administered in the form of a suspension to children. After three to four days, if the clinical response was satisfactory, the dose was halved and given as a single daily dose. Treatment was given for 3–4 days in 2 cases, 5–6 days in 9 cases, and 7–14 days in 7 cases.

There was one striking case of resistant proteus infection which responded to this sulphonamide. This occurred in a woman following hysterectomy, and the laboratory report showed that the organism was only sensitive to streptomycin and nitrofurantoin, being resistant to sulphafurazole, the sulphonamide used for testing. In spite of this the urine became sterile after two weeks' treatment with sulphaphenazole, and there has been no recurrence in the several months since then.

With regard to side-effects, these were minimal. One patient complained of drowsiness, another of "spots in front of the eyes," and three of mild gastric irritation. These side-effects were trivial and no bar to continued treatment.

It is apparent from these results that sulphaphenazole is an effective sulphonamide for use in the treatment of acute genito-urinary infection in general practice. It has the advantage of prolonged length of action, and in this small series of cases did not give rise to any significant side-effects. The published work on this drug would seem to verify the claim that it is virtually free of any serious side-effects. This being the case, it might be a suitable and cheaper alternative to long-term tetracycline in the prophylactic treatment of chronic bronchitis. It is our intention to conduct a further trial of this sulphonamide for this purpose during the coming winter months.

I am indebted to Dr. D. Clarke, of Streatham, London; Dr. J. C. Merry, of Exeter, Devon; Dr. D. J. Morton, of North Berwick, Scotland; and Dr. D. R. Wright, of Colnbrook, Bucks, for assisting in this investigation.

—I am, etc.,

Twickenham. David Wheatley.

Belated Diagnosis of Hashimoto's Disease

Sir,—In clinical practice re-diagnosis is common. However, a convincing new diagnosis made more than 60 years after the onset of disease may have some especial interest.

In May, 1896, the patient, a housewife aged 29, was admitted to the Middlesex Hospital with a provisional diagnosis of bronchocele. At that time she complained of increasing swelling of her neck and loss of voice for eight months. The only abnormal physical signs were a whispering speech and goitre. Both lobes and the isthmus of the thyroid gland were hard and not tender. She was given thyroid extract, improved, and went home with a month's supply of three tablets of thyroid extract daily.

In 1904, at the age of 37, she was seen in the out-patient department for her complaints of puffy eyes, swollen face, giddiness, stiffness of the fingers, and constipation. Myxoedema was diagnosed. The symptoms responded to thyroid, and she has remained well, apart from minor fluctuations of hyper- and hypothyroidism, on a dose of 1½–6 gr. (0.1–0.4 g.) per day. The only metabolic studies were in 1942, when her basal metabolic rate fell from −3% to −19% (Aub–DuBois) after three weeks without thyroid tablets.

In February, 1959, at the age of 92, after a total of over 70,000 gr. (10¼ lb.—4.7 kg.) of thyroid extract, she was symptom-free, active, and clinically euthyroid when she attended hospital for the 372nd time. Her old notes were studied, and it was considered that in 1895 she must have had lymphadenoid goitre (described by Hashimoto in 1912 as struma lymphomatosa), which disease and its associated myxoedema had been controlled ever since by thyroid therapy. It was fascinating to discover, even after 63 years, a trace (1/5) of thyroid auto-antibody with the tanned red-cell agglutination test.

I wish to thank Dr. G. D. Hadley for his advice and permission to publish, and Dr. Deborah Doniach for the serological studies.

—I am, etc.,

The Middlesex Hospital, London, W.1 J. H. BARON.

Insect Stings

SIR,—From your annotation (*Journal*, September 12, p. 417) it does not seem to be generally known that the severity of the symptoms due to insect stings bears direct relation to the *site of injection* of the venom. Whereas a subcutaneous injection may lead to serious symptoms in an allergic subject, direct injection into a vein can cause rapid, extremely serious results. For instance, a wasp-sting penetrating a temporal vein can lead within three minutes to acute cardiac pain, nausea, and collapse of the victim, and be so alarming that death appears imminent. With suitable and immediate treatment, the condition passes and within an hour the patient may be entirely recovered. This condition seems to be in no way connected with allergy, for the subject may have been previously, and subsequently be, stung by wasps with no results but transient local pain.

A heavy intravascular injection of venom without treatment may be the explanation of sudden death in those anomalous cases in which many previous stings from the same species of insect have led to no serious effects. The clinical importance of recognizing the difference between direct cardiac poisoning and an allergic manifestation will be obvious.—I am, etc.,

Rotherfield, Sussex. INNES H. PEARSE.

The Customary Fee

SIR,—With reference to Mr. W. R. Smith's letter (*Journal*, September 26, p. 583), it would appear that the consultant treated the retired doctor for three and a half weeks at the local general hospital and a further five and a half weeks in the convalescent home, making a total of nine weeks, for which a charge of 60 guineas does not seem "such a heavy fee." What is involved here is the principle of one doctor charging another doctor and a retired one at that. Being retired myself, this matter interests me considerably. Is this not a thing in which the B.M.A. should interest itself and publish its views?

I feel sure when a retired doctor takes out an insurance against illness he is thinking only of the charges for a private ward. I myself have never given a thought to attending physician's or surgeon's charges, and this letter from Mr. Smith indeed comes as a timely warning of what I may expect.—I am, etc.,

Wimbledon, London, S.W.19. B. J. BOUCHÉ.

SIR,—I am surprised that any medical man should charge another doctor for his services, especially one who has retired (*Journal*, September 26, p. 583). I too am a retired G.P. In all my practising life neither I nor my partners ever charged a fee to a medical man, nor to the best of my knowledge did my forebears, nor does my son, my daughter, or my son-in-law. Doctors' widows were never charged, nor were parsons, priests, or ministers of religion. In rare cases where there were adequate means and accounts were insisted on, then they were sent in. In some cases doctors gave one presents at Christmas-time in gratitude, and one appreciated the thought very much.

In recent years I have needed the ministrations of consultants, but there was never a suggestion of a fee. I gave them presents, but I am absolutely certain that those presents were quite unexpected. Anyway, they were merely tokens of my appreciation of all the skill and kindness that I received. I had to pay the usual rate for a private ward and for laboratory services and the like. In the old days I would not have been so charged; that was traditional, but there is little sentiment in an Act of Parliament.

Can it be that this consultant's accounts are handled by a secretary, and that she did not appreciate the situation and sent out the account in ignorance? That is no excuse, but it may be an explanation.—I am, etc.,

ANOTHER RETIRED G.P.

Cardiac Arrest

SIR,—In view of recent correspondence on recovery after cardiac arrest, the following case may be of interest.

This was the mother's third pregnancy, and gestation was normal save for strong antibody production. Delivery was complicated by arrest of the foetal chin behind the symphysis, which necessitated manual interference only. The baby's condition following delivery was excellent. At birth the Coombs test was strongly positive and the haemoglobin 80%. Serum bilirubin was 2.2 mg./100 ml. Birth weight was 8 lb. 12 oz. (3.07 kg.).

An immediate exchange transfusion was given. After the first pint (0.6 litre) of blood the baby's condition was satisfactory (colour, heart rate, etc.), but after half of the second pint of blood (that is, when 0.9 litre had been exchanged) its condition was noted to be deteriorating slightly and bradycardia was noted. It was decided to exchange a further 40 ml. only, but after half this quantity the baby collapsed, the heart stopped, and a mild left facial paresis occurred.

Treatment consisted of artificial respiration, mouth-to-mouth breathing, and intracardiac adrenaline. The pulse returned—though somewhat slowly at first. The next day occasional Jacksonian movements of the left arm, leg, and face were noted. Thereafter progress has been quite normal and no sign of permanent neurological damage, as yet, has been detected.

It was thought arrest was due to hyperkalaemia, an ever-present threat during this procedure.—I am, etc.,

West Park Hospital, Macclesfield, Cheshire. GRAHAME SUTTON.

SIR,—Is it a coincidence that so many of the cases of cardiac arrest described in recent correspondence were induced with thiopentone and suxamethonium chloride? It is easy to criticize, and difficult to decide what is the best anaesthetic for a seriously ill patient:

but I cannot help feeling that a little more caution regarding the use of suxamethonium chloride for bad-risk cases might result in fewer patients requiring cardiac massage.—I am, etc.,

Newcastle upon Tyne PHILIP AYRE.

Service Psychiatrists

SIR,—I am intrigued that you should devote so much of your precious space to a review of *Psychiatry in the British Army in the Second World War* (*Journal*, September 26, p. 551). More than a whole page, or over 1,200 words, is a lot compared with the average of 200–400 words with which most reviews have to be content. Can it be that Professor F. A. E. Crew feels it is necessary to justify the activities of those "young men who . . . were quite outstanding in respect of their intellectual equipment, their professional competence, and their ability to adjust themselves to the conditions and circumstances of an entirely novel world"? With sadness he recalls that they were dubbed trick-cyclists, "a pejorative term used by some to convey their amused contempt and by others to express their frank and somewhat venomous hostility." He adds that opposition came not only from the topmost levels of the military hierarchy but even from colleagues in other branches of medicine. He might even have quoted the views of General Patton on this subject.

It is not to be supposed that the psychiatrists in the Royal Air Force were any less brilliant than their Army brothers.

At the end of a lecture on "Flying Stress" a wing commander psychiatrist called for questions. A young bomber navigator asked a somewhat technical question about ditching a plane. To the embarrassment of all, the specialist admitted that he had never been on an operational station.

A flying officer (aircrew) was worried about his wife's dyspareunia, and an appointment was requested at a near-by R.A.F. hospital to which a gynaecologist paid a monthly visit so that he might discuss his marital difficulties. Unhappily a psychiatrist also visited this hospital on the same day. The flight sergeant appointments clerk scratched his head and asked himself what for could a Spitfire pilot need a gynaecologist's advice. So he booked him to see the psychiatrist. Faced by a squadron leader, the flying officer answered the strange and, it seemed, inappropriate questions which were put to him, and was even more surprised to be dismissed without help or comfort but with the assurance that a report would be sent to his commanding officer. From then on the wheels turned quickly. A medical board was held in London, and, but for the intervention of some very, very cross flying men at Group Command, the flying officer would have found himself in civilian clothes. At his own request the psychiatrist was posted to another hospital: our mess was quite looking forward to his next visit.

Shortly after the liberation of Brussels the city was being bombarded by V.1.s. A medical board was in progress on an army sergeant whose case was diagnosed as Lack of Moral Fibre. He was standing stiffly at attention in front of a table, behind which sat a psychiatrist and two other doctors. As the motor of the doodle-bug cut out all three dived under the desk, and later it was a matter for argument who got there first. When the noise of the explosion died away they surfaced, somewhat sheepishly, to find the sergeant still at attention.

Sir, the Service psychiatrists were not all that wonderful. In the main we smiled at them and some of them were able to smile at themselves. On balance they probably did as much good as the undoubted harm they also did. Professor Crew quotes with satisfaction the approval which the adjutant general and the D.G.A.M.S., Sir Alexander Hood, bestowed on the Directorate of Army Psychiatry: but there was at least one V.I.P.[1] who held other views:

"*Prime Minister to Lord President of the Council.* December 19, 1942.

"On August 4, 1942, the War Cabinet set up a Ministerial Committee . . . to supervise the work of an expert committee on the use made of psychologists and psychiatrists in the Fighting Services.

"I am sure it would be sensible to restrict as much as possible the work of these gentlemen, who are capable of doing an immense amount of harm with what may very easily degenerate into charlatanry. The tightest hand should be kept over them, and they should not be allowed to quarter themselves in large numbers upon the Fighting Services at the public expense. . . . There are quite enough hangers-on and camp-followers already."

Professor Crew writes in his review that the Army psychiatrists had "to contend with considerable opposition born of misunderstanding and prejudice." Cannot psychiatry rid itself of its inferiority complex and learn the virtue of humility?—I am, etc.,

London, S.W.7. MICHAEL HARMER.

REFERENCE

[1] Churchill, Winston S., *The Second World War*, Vol. 4, Appendix C, p. 814, 1951. London.

Micturition after Prostatectomy

SIR,—Those like myself who have had a successful prostatectomy may not know a simple way of completely emptying the urethra after micturition. I discovered it quite accidentally some months ago. Merely emptying the penile urethra is not enough; there may be "dribbling" of urine for minutes afterwards, which is very annoying. The way to prevent this from happening is firmly to press upwards on the perineum after the bladder has been emptied. This completely empties the whole urethra. I have never heard of this advice being given to prostatectomy patients.—I am, etc.,

Penarth, Glamorgan. LESLIE B. C. TROTTER.

The Occasional Obstetrician

SIR,—It was refreshing to read some practical common sense on the subject of domiciliary obstetrics in the *Journal* of September 12. I refer to letters from Dr. B. W. Perlow (p. 432) and Dr. J. B. Wigdahl (*Supplement*, p. 88). I very much agree with all they said. Dr. Perlow deplored the loss of that "intangible of life," the doctor–patient relationship of confidence of the woman in labour. This sort of thing has been talked of ever since the inception of the N.H.S. Obviously, the committees still regard it as mere sentimental and outmoded nonsense. Their plans will all come to nothing, because it is the most important factor in all medicine, and especially applicable in pregnancy and labour.

Even when under G.P. supervision hospitals are quite the wrong places for the practice of normal obstetrics. Personal and unhurried care is never obtainable in them, nor ever will be. In all the hospitals that I know the expectant mother always assumes the role of a sausage in a sausage-machine. There never will be any substitute for home as the ideal place for normal midwifery.

The hospitals must concentrate on three things. They must improve their care of the abnormal or complicated case; there must be a considerable improvement in their

attitude to patients by regarding them as individual personalities; they must strive to lower the incidence of post-partum infection of mother and child. We all know how much more of the latter occurs in hospital than at home. The following groups of people should be confined at hospital: (1) Those who have medical grounds. (2) Those with a bad obstetrical history. (3) Those with some abnormality of pregnancy. (4) Those living in an inadequate home or very isolated and remote place, or where other social reasons obtain. (5) A primigravida who is very nervous, or who has a strong, insistent preference for hospital. (6) Those with a multiple pregnancy. (7) Some cases of multiparity.

The great majority can be perfectly well looked after by the family doctor and midwife in conjunction. Their excellent management is a reflection of those who taught them.—I am, etc.,

Saffron Walden, Essex. J. D. C. Cook.

Telling the Cancer Patient

Sir,—Your correspondence on this subject has been stimulating. The letter from Dr. Wm. J. O'Connell is particularly so (*Journal*, September 19, p. 503).

It causes me to ask, "Why is there any reason for this discussion?" The answer is that the patient fears the disease and perhaps even more the means—surgery and radiotherapy—adopted to treat it. When we have a scientific means for cure the fear of the disease will go, and the fearful, useless, extensive, mutilating, and dangerous operations will cease to be performed. Our surgical philosophers, from Hippocrates onwards, have warned us against these, and the sooner they are stopped the better, for, as in tuberculosis, they will one day cease to be performed, and will be regarded as curiosities of the past.

The duty of the doctor is clear—he must tell the truth if he is asked for it. If the patient has the fear of cancer—and there are many who have and yet have not got it—he will welcome the advice of the good doctor, "There is no sign of cancer," particularly if he can be given adequate explanation of the signs and symptoms and by treatment causes them to disappear. If the signs and painful symptoms are such as have led to scientific investigations which suggest cancer, with our present inadequate knowledge some measures will have to be devised to give relief; and the patient will respect the doctor for giving him that treatment which gives relief, since this has been successful with his friends. But even when the case is inoperable the patient should be encouraged to be persistently hopeful—indeed, the very signs which cause the surgeon to abandon surgery will be proved to be beneficial. I have seen complete recovery in a case where the radiograph of the chest showed multiple secondaries in the lungs the day before the operation, a forequarter amputation of the right limb, and caused the surgeon to urge no treatment. This was good radiography, for it spared the patient pain, whereas that radiography which incites the infliction of unnecessary mental or physical pain is bad radiography. Miracles still occur—for this we have the testimony of such men as Sir Thomas Browne and Sir William Osler. Who am I to dissent? From a careful study of these miracles—they occur in all spheres of human and animal existence—we would learn much more than from the useless, non-instructive mutilations which have prevented us from studying the natural history of the disease.—I am, etc.,

Birmingham, 15. James F. Brailsford.

Forgotten Swabs

Sir,—Another death, due to a swab left in the abdomen following an operation, has recently been reported.

Might I suggest that it should not be beyond the imagination of the surgical instrument companies to produce a simple machine, on the lines of the ordinary office stapler, which could be sterilized and used in the theatre to punch a small metal staple or clip into the corner of every swab? The staple, or clip, should be of some metal, such as tantalum, acceptable by the tissues, and the machine should register the number of staples inserted and, therefore, the number of swabs used. If there is any doubt at the end of the operation as to how many swabs had been used and the possibility of any being left in the patient, an *x*-ray examination would give the answer.—I am, etc.,

Bangor. T. G. Wynne Parry.

Skin Disinfection

Sir,—In an annotation on skin disinfection (*Journal*, May 30, p. 1398) a most interesting account of the search for the ideal antiseptic is given. Mention is made of various workers in this quest, beginning with Senn's article in 1905,[1] and Epstein's article in 1897,[2] right up to Frisch, Davies, and Krippaehne in 1958.[3] The annotation states, "There is need for an antiseptic which is free from irritant or sensitizing properties and equal or superior to alcoholic iodine in its ability to disinfect skin," and later, "Careful comparative studies of alternative methods by a reliable technique are needed . . . but the factors which determine sepsis are numerous and it is not surprising that published data on the protective role of skin disinfectants are inconclusive."

May I draw your attention to an antiseptic (i.e., tincture of phenylmercuric dinaphthylmethane disulphonate) ("penotrane") which fulfils the two desiderata of your first paragraph which I have quoted? The reference for the experimental investigations is given in Reid *et al.*,[4] and a list of further references is given below.[5–7] Some other factors are also worth noting—namely, that penotrane penetrates to all layers of the dermis and even into the subcutaneous tissue; it is effective in high dilution against all the bacteria and fungi likely to be encountered in the skin; it is adsorbed on to the cells of the skin so that the local concentration builds up and remains high for a long time, and its activity is somewhat enhanced in the presence of protein material such as blood, serum, and pus.—I am, etc.,

Liverpool, 1. Hugh Reid.

References

1. Senn, N., *Surg. Gynec. Obstet.*, 1905, **1**, 1.
2. Epstein, F., *Z. Hyg. Infekt.-Kr.*, 1897, **24**, 1.
3. Frisch, A. W., Davies, G. H., and Krippaehne, W., *Surg. Gynec. Obstet.*, 1958, **107**, 442.
4. Reid, H., Black, T., and Dean, D., *Practitioner*, 1958, **180**, 707.
5. Goldberg, A. A., Shapero, M., and Wilder, E., *J. Pharm. (Lond.)*, 1950, **2**, 20, 89.
6. Haler, D., *Antibiot. Med., Brit. Ed.*, 1957, **2**, 358.
7. Tiessen, H. J., *Derm. Wschr.*, 1957, **135**, 548.

Gravel Rash

Sir,—Casualty officers usually find that removing embedded dirt from "gravel rash" is a slow and painful task. It may be made easier by applying lignocaine 4% ("topical xylocaine") for several minutes. The area can then be scrubbed painlessly.—I am, etc.,

Hornsey Central Hospital, London, N.8. G. Heap.

Obituary

JOHN KIRK, M.B., F.R.C.S., F.R.C.S.Ed.

Professor John Kirk, professor emeritus of anatomy in the University of London, died peacefully in his sleep at his home at Stanmore, Middlesex, on September 26. He was 77 years of age.

John Kirk was born on November 27, 1881, the son of the Rev. John Kirk, and was educated at George Watson's College and at Edinburgh University, where he graduated M.B., Ch.B. in 1904. During the course of his student career he was twice awarded medals in practical anatomy and prizes in systematic and clinical surgery. After graduation he held the appointment of house-surgeon at the Mildmay Mission Hospital, Bethnal Green, before going to New Zealand in 1906. From then on until 1928 he was engaged in medical missionary work in China under the New Zealand Presbyterian Mission. He became a lecturer in human anatomy at the Kung Yee Medical College, Canton, and in 1924 was placed in charge of the new department of anatomy, the first of its kind in South China. While on leave in 1914 he was admitted a Fellow of the Royal College of Surgeons of Edinburgh, and during his second furlough in 1921–2 he worked as a full-time demonstrator in anatomy in Birmingham University. For six years he was a member of the council on medical education of the Chinese Medical Association, and was president of this association from 1923 to 1925. In the latter year he was chairman of the joint conference on medical education arranged by the Chinese Medical Association and the Hong Kong and China Branch of the British Medical Association.

In 1928 he returned to England and was appointed a full-time demonstrator in anatomy at University College, London, becoming senior demonstrator in 1930. Later he became sub-dean of the faculty of medical science at the college, senior tutor in the faculties of medicine, science, and engineering, and lecturer in anatomy to the Slade School of Fine Art. In 1937 Kirk was appointed to the S. A. Courtauld chair of anatomy at Middlesex Hospital Medical School, in succession to Professor Thomas Yeates, and occupied the chair until 1949, when he retired. The title of professor emeritus was then conferred upon him. From 1943 to 1945 he was secretary of the board of studies in human anatomy and morphology, and he was chairman of the board from 1945 to 1947. In the service of medical education he was chairman of the committee of anatomical supply for the London area from 1937 to 1947, and he had been chairman of the committee of licensed teachers of anatomy in Great Britain. He was honorary treasurer of the Anatomical Society of Great Britain and Ireland from 1937 to 1947, and a vice-president of the society from 1947 to 1949. He was admitted a Fellow of the Royal College of Surgeons of England in 1952. A member of the British Medical Association for over fifty years, he served as president of the Section of Anatomy and Physiology when the Association held its Annual Meeting at Harrogate in 1949.

E. W. W. writes: By the death of John Kirk the University of London has lost a much-loved professor emeritus, and countless men and women throughout the world a true and warm-hearted friend. In the medical school where he graced the chair of anatomy for 12 years he will be remembered not only as a magnificent teacher but as a great gentleman whose influence amongst staff and students alike was wholesome as the sunrise. Tall and handsome, he combined a natural dignity with a deep humanity and abounding good humour, such that even a momentary encounter left one feeling that the world held much that was rich and splendid. To look upon him was to catch a glimpse of the rugged grandeur of his native mountains, and to feel again the fresh invigorating wind across the moor.

To those who were privileged to work at his side he was a fount of deep wisdom and a source of unfailing kindness. Thorough in everything he undertook, he drove himself hard. Nothing was done for effect; no histrionics marked his lectures or demonstrations, but for all that the hour sped past. With his vast store of clinical experience to draw upon—experience gained amongst the people of China to whom he gave half his working life—he selected wisely those practical considerations which so quicken the student's interest. This said, it must not be thought that he saw the science of anatomy merely as the handmaiden of surgery, for to him it was an equal partner with its own contribution to make to the advancement of learning.

His superb knowledge of human anatomy was perhaps revealed at its best in the courses which he gave to Primary Fellowship candidates. Here was no armchair anatomist but the practical master of his subject, and for those who sat at his feet—and they came from every corner of the globe—anatomy took on a fresh lustre.

For more than 30 years Professor Kirk was a member of the Anatomical Society of Great Britain and Ireland, and held office as vice-president and as treasurer; in 1949 the Society honoured him by election to life-membership. His research interests centred, very naturally, on problems having a direct clinical bearing, but any genuine worker in the anatomical field, however pure his research, could always count on his full support and encouragement.

Retirement for J.K., as he was affectionately known, soon found him hard at work again; nor in the nature of things could anything else have been expected. Responding to the invitation of the General Medical Council to act as their Visitor, he spent some years inspecting in turn every department of anatomy in Great Britain and Ireland. These occasions were a source of immense pleasure both to the Visitor and to those who received him; and that his reports later proved comprehensive, fair, and helpful might well have been forecast.

It seems strange that we shall no longer see him striding up the fairway in the staff–student golf matches, or hear his carefully uttered views in our councils; but so it is, and in our sorrow we extend our deepest sympathy to the lady who was his wife for more than 50 years, and to his sons and daughter.

W. E. GALLIE, M.D., Sc.D., F.R.C.S., F.R.C.S.Ed., F.R.C.S.C., F.A.C.S.

Professor W. E. Gallie, emeritus professor of surgery in the University of Toronto, died at Toronto on September 25. He was 77 years of age.

William Edward Gallie was born at Barrie, Ontario, on January 29, 1882, and was educated at Toronto University, where he graduated M.D. in 1903. After graduation he held resident appointments at the Hospital for Sick Children, Toronto, and at Toronto General Hospital, and he continued to serve these hospitals to the end of his active career. He became consulting surgeon to both institutions, having been chief surgeon of the former from 1919 to 1929 and of the latter from 1929 to 1947. In Toronto University he progressed from junior demonstrator in anatomy in 1906 to demonstrator in pathology (1909–12), and from thence to assistant professor of surgery (1919–29), and to professor of surgery and head of the department from 1929 to 1947. He was also dean of the faculty of medicine from 1936 to 1946. When he retired in 1947 the title of emeritus professor of surgery was conferred upon him.

Elected a Fellow of the Royal College of Surgeons of England in 1918, he delivered in 1924 a Hunterian lecture before the College on the transplantation of the fibrous tissues in the repair of anatomical defects. In 1947 he delivered a Moynihan lecture on recurring dislocation of the shoulder, and in the same year he was awarded the

honorary gold medal of the College. He attended the twelfth congress of the International Society of Surgery in London in 1947 and spoke on heparin in surgery. A Fellow of the Royal College of Surgeons of Canada, he was also a Fellow of the Royal College of Surgeons of Edinburgh, and of the American College of Surgeons, of which he was a past-president. An honorary Fellow of the Royal Society of Medicine, and of the Association of Surgeons of Great Britain and Ireland, he was also a past-president of the American Orthopaedic Association and of the American Surgical Association, and he was an honorary member of the British Orthopaedic Association. He acted as a vice-president of the Section of Orthopaedics at the Centenary Meeting of the British Medical Association held in London in 1932. In 1948 McGill University conferred upon him the honorary degree of Sc.D. In 1914 he married Janet L. Hart, by whom he had two sons and one daughter.

Sir GORDON GORDON-TAYLOR writes: September 25, 1959, was remarkable for two widely different events in surgical history: the demi-centenary of the Moynihan Surgical Club, an occasion appropriately celebrated in the city of Leeds, and the passing of the famous Toronto surgeon, Edward Gallie, a surgeon of international fame. For upwards of 40 years Gallie's contribution to surgery had attracted the attention not only of Canada but of the whole surgical world, and from 1929, when he became professor of surgery and head of the department of surgery in the University of Toronto, till 1946, when he resigned from the professorial chair and the deanship of the faculty of medicine, he seemed to bestride the surgery of Canada like a colossus. Yet colossus scarcely describes the man, since, despite his towering height and gigantic frame and the vastness of his influence in matters that concerned Canadian surgery, including surgical appointments, surgical training, and surgical research, there was always a twinkling cheerfulness about "Ed" Gallie. His surgical stature was recognized beyond the shores of Canada, and he remained President of the American College of Surgeons for six years, the longest presidency of any surgical college except that of the late Lord Webb-Johnson in Lincoln's Inn Fields.

Not only was Gallie a Hunterian professor and a Moynihan lecturer at the English College of Surgeons, but in 1947 he received its highest award, the honorary medal, for "distinguished labours, researches and discoveries, eminently conducive to the improvement of natural knowledge and of the healing art." On the occasion of the visit of the Gallie Surgical Club to Britain in 1957, when Gallie was 75 years old, the Royal College of Surgeons of Edinburgh conferred its honorary fellowship upon him.

As behoved a professor of surgery in a great university, Gallie had a keen interest in every department of surgery, but the nature of his enduring contributions to the advancement of the science and art of surgery shows that it was reparative surgery that fascinated him most. The chief of these communications to surgical literature are concerned with tendon fixation, whereby he converted the tendon of a paralysed muscle into a check ligament by implanting its upper segment into the bone proximal to the articulation whose movement the tendon normally controls. Secondly, there were his contributions to our knowledge and our treatment of injuries of bone with special emphasis on the transplantation of bone. Thirdly, there was his work on fascial transplants which was to exercise a lasting influence on surgical technique. Perhaps, however, his greatest contribution was his stimulating interest and his encouragement to the young surgeons. Surgical aspirants jostled each other to become attached to his surgical unit: to be elected a member of the Gallie Club was the greatest honour that a surgeon could boast. I only know of one English member, Anthony Till, of Oxford, who is proud of the cachet that such membership confers across the North Atlantic.

Gallie's period of surgical activity coincided with a golden age in Toronto's scientific history: it was the era of "Fred" Banting and "Charlie" Best, who brought salvation to the diabetic: it was the period of the development of the heparin project and its availability for clinical use, thanks to the work of Best, Scott, Charles, and Gordon Murray: it was the period of early blood transfusion in which Bruce Robertson played so important a role in the first world war: it saw in Toronto the pioneer operation for an "islet"-tumour of the pancreas: it witnessed the work of "Eddy" Robertson at "The Children's," the pioneer surgery of Norman Shenstone in the thorax; of Arthur LeMesurier, Gallie's fellow-researcher in many surgical problems, with his special interest in cleft palates; of Harold Wookey, with his work on malignant disease of the mouth and pharynx; and many others. To all these, his contemporaries and colleagues, Gallie was a benevolent dictator lending encouragement and inspiration. The spirit of research whose flame he fanned so vigorously and unceasingly still blazes in Toronto, and Gallie remained youthful to the end, thanks to his abiding interest in surgical progress, more especially in the achievements of those who were his pupils, men like Bigelow, Mustard, Gordon Murray, and others. The work of those who were his successors in the deanship and the professorial chair must have afforded him immense satisfaction: MacFarlane, "Bob" James, Fred Kergin—were they not his own pupils and friends?

To surgeons everywhere the mere mention of Ontario's great city has long inevitably, instantly, automatically brought the name of Gallie to mind and to the lips. Memorials are of many kinds: a piece of surgical cutlery is an unworthy talisman to surgical immortality, though Gallie has a needle that bears his name: operative techniques, too, have their vogue till time relegates them to the limbo: the eponymous postgraduate curriculum for would-be surgeons will doubtless be modified or changed, but I am confident that the surgical club which his colleagues and pupils instituted to honour him will perpetuate his memory for all time, like those in Britain which bear the honoured names of Robert Jones and Moynihan, for the Gallie Club meets each year on his birthday "for intellectual stimulus and good fellowship." At this sad moment, while Toronto, Ontario, Canada, mourn the loss of a distinguished Canadian, the whole world of surgery grieves at the death of one of the very greatest master surgeons of all time.

J. C. S. writes: News has just arrived of the loss of one of the greatest of Canadian surgeons, and those who were privileged to know him will feel a deep sense of personal loss. W. E. Gallie was justly famous for his prowess as a surgeon, and his great contributions to the science and practice of surgery are universally well known and appreciated. He will be long remembered and revered for his advances in medical education—particularly postgraduate surgical training. These qualities, great as they were, were overshadowed in all contacts with his pupils by his endearing and inspiring personality. There are many, like myself, who owe much to the advice, assistance, example, and friendship of this great and modest man.

W. F. CROLL, M.D.

Dr. W. F. Croll, honorary consultant physician to Aberdeen Royal Infirmary, died at his home at Aberdeen on June 21. He was 84 years of age.

William Flett Croll was born at Aberdeen on September 17, 1874, and was educated at Aberdeen Grammar School and the University of Aberdeen. He graduated M.A. in 1895, M.B., Ch.B. in 1900, and M.D., with honours, in 1908. For a number of years he was an assistant in the materia medica department of Aberdeen University, and afterwards physician to Aberdeen Royal Infirmary and lecturer in clinical medicine in the university. He took an active part in the Aberdeen Dispensary and Vaccine Institute and for many years was chairman of the committee of management.

Dr. Croll was early interested in cardiology, and in 1920 he was the first physician in charge of the cardiograph

department of the Aberdeen Royal Infirmary. The students of the 1920's and 1930's will remember his methodical clinical teaching, his upright bearing, commanding personality, and his playful humour. In his youth he was an outstanding athlete, a very good boxer, a strong swimmer, and an accomplished high diver. He took an active part in the university sports, and was generally in the field as a judge or time-keeper. His last years, after the death of his wife in 1950, were none too happy because of spells of severe mental depression, and he spent his time reading and taking quiet walks in the country.—R. J. D.

B. PICKERING PICK, C.B.E., M.R.C.S., L.R.C.P.

Surgeon Rear-Admiral B. Pickering Pick, who, in the course of a long career in the Royal Naval Medical Service, was one-time professor of surgery at Haslar Hospital, died in his sleep at his home at Sherborne, Dorset, on July 3. He was 79 years of age.

Bryan Pickering Pick was born on September 13, 1879, the son of Mr. T. Pickering Pick, F.R.C.S. From Sherborne School he became a medical student at St. George's Hospital, qualifying M.R.C.S., L.R.C.P. in 1904. Entering the Royal Navy immediately after qualification, he served for thirty-four years, and at various times was principal medical officer at Dartmouth, professor of surgery at Haslar Hospital, and medical officer in charge of the Royal Naval Hospital, Chatham. During the first world war he served in hospital ships. Appointed O.B.E. in 1928, by which time he had attained the rank of surgeon commander, he was promoted C.B.E. in 1938, the year in which he retired with the rank of surgeon rear-admiral. In 1936 he was appointed an Honorary Surgeon to the King. From 1939 to 1946 he was house-governor and medical superintendent of the King Edward VII's Convalescent Home for Officers, East Cowes, Isle of Wight. He served for a term (1938–9) on the Council of the British Medical Association, and was president of the Kent Branch of the Association in 1936–7 and chairman of the Isle of Wight Division in 1944–5. A governor of his old school, he edited the fourth edition of the *Sherborne Register*, and was secretary of the Old Shirburnian Society. He leaves a widow.

GEORGE CAHILL, M.D., D.Sc., F.A.C.S.

Dr. George Cahill, formerly professor of urology at the School of Medicine of Columbia University, New York, died on July 24, aged 69.

George Francis Cahill graduated in medicine at Yale University in 1911, and not long afterwards he became an instructor in surgery at New York University. During the first world war he served with the British 3rd Army, with the French Army, and finally he was commanding officer of a base hospital of the American Expeditionary Force. Shortly after his return to New York he was appointed professor of urology at Columbia University. He was a governor of the American College of Surgeons and president of the medical board of the Presbyterian Hospital.

Mr. Clifford Morson writes: The death of George Cahill has removed a distinguished figure from the field of international urology. He succeeded Bentley Squier as chief urologist to the Presbyterian Hospital in 1917 and soon established himself as one of the leaders in this branch of surgery in North America. Cahill resigned this appointment in 1955 on reaching the age limit of 65. In that year he was honoured by Columbia University with the honorary degree of Doctor of Sciences. The gold medal of the Society of Genito-urinary Surgeons, an award much prized by our American colleagues, was presented to him in 1957. He was an honorary member of the Canadian Urological Association.

British urologists who had the privilege of Cahill's friendship will never forget his generous hospitality in the beautiful home at Suffern, 20 miles from New York City. He delighted to attract the many colourful varieties of birds which can be seen in the State of New York into his garden, where they made full use of the feeding-boxes hanging from the trees. He would point out to his guests how the little chipmunk dashed from his hide-out in a bush to collect any pieces left over on the lawn.

Urologists in many lands will regret the passing of George Cahill. Their sympathies go out to his widow, Eva.

C. J. B. WAY, *M.C.*, M.B., B.S.

Dr. C. J. B. Way, who had been in practice in Golders Green since the end of the first world war, died at his home there on August 8, at the age of 67.

Cyril James Berkeley Way was born on June 20, 1892, the son of T. R. Way, artist and lithographer, of Primrose Hill. He was educated at William Ellis School, Gospel Oak, and at the Middlesex Hospital. At the outbreak of war he hastened to qualify, taking the L.M.S.S.A. in the autumn of 1914. He served with distinction with the 50th Field Ambulance, R.A.M.C., being awarded the Military Cross and twice mentioned in dispatches. After the war he graduated M.B., B.S., and set up in practice in Golders Green. He was connected for a while with the Hampstead General Hospital, acting as assistant to the late Mr. Lawson Whale. He was police surgeon for some years, and until his death medical officer to the Hendon District Hospital. Since 1953 he had been medical referee to the Golders Green Crematorium and became the first president of the Association of Crematorium Referees, which he had helped to found. An active member of the Hendon Division of the B.M.A., he was for a long while clinical secretary of the Division. He was also a liveryman of the Worshipful Society of Apothecaries and a Freeman of the City of London.

His practice was a successful and happy one, enriched by his hospitality, his many friends, and his wide tastes in modern art, music, and literature. Over the last six years he suffered three attacks of coronary thrombosis, but always returned with vigour to his practice. Despite failing health recently, he stayed at work until the very end, having completed his round an hour before his death. He is greatly missed by a wide circle of friends and patients. He leaves a widow, a daughter, and a son, who is also a doctor.

R. BATHGATE JOHNSTON, F.R.C.P.Ed., F.R.C.S.Ed.

Dr. R. Bathgate Johnston, who was in general practice for many years, first at Penrith, Cumberland, and then in London, died on August 11 at Salisbury, Southern Rhodesia, where he had been living in retirement. He was 87 years of age.

Robert Bathgate Johnston was born on May 28, 1872, and received his medical training in Glasgow, taking the Scottish triple qualification, with honours, in 1902. In 1904 he took the F.R.C.S. of Edinburgh, and in 1912 the M.R.C.P. of Edinburgh, being admitted a Fellow in 1919. He was also a Fellow of the Edinburgh Obstetrical Society. After qualification he held appointments at Edinburgh Royal Infirmary, the Simpson Memorial Maternity Hospital, and at the Chalmers Hospital, Edinburgh. He was for a time demonstrator in anatomy at the Royal College of Surgeons of Edinburgh. From 1904 to 1920, except for the period of his service in the first world war, he was in practice at Penrith. During the war he was a surgical specialist in the 81st General Hospital, with the rank of major in the R.A.M.C. In 1922 he moved to London, where again he was in general practice until 1947, when he retired. In the following year he and his wife went to live in South Africa, later moving to Southern Rhodesia.

J. M. writes: I worked with, and was in close and valued personal contact with, Bathgate Johnston for all of the past 30 years, except for the war years. He was my nearest medical colleague in London (Streatham Hill), and I have

not forgotten his comment to me in 1929 to the effect that in competitive medical practice "there was no room for sentiment but that harmony was essential." The harmony was such that before very long we found we could relieve each other during holidays or illness and never required the services of a locumtenent. I understand that after his hospital work in Edinburgh he was offered the first chair of surgery in the new Cape Town University and also the chair of surgery at St. Andrews University, but decided to devote his service to general practice. In Penrith he had a widespread general and surgical practice, so much so that he had to maintain a stable of six horses, and in the winter he travelled by horse and sleigh.

Dr. Johnston was singularly fortunate in, and happy and proud of, his family, and was blessed indeed in the care, love, and devotion of his wife, Gertrude. This was particularly demonstrated in the last year of his life, when he had to submit to, what was to him, the indignity of the amputation of a leg on account of arterial sclerosis. Bathgate, apart from his many qualifications and medical successes, was a typical Scot, of the sturdy, straightforward, and forthright type, to whom snobbishness, humbug, and pretence were anathema. He was kindly to the point of affection with his patients and upright in all his dealings. His interest in medicine never flagged, and his anatomical knowledge was keen and acute to the last. With his passing there goes from the scene an outstanding figure characteristic of all that is good and worth while in what to him always was a noble profession.

ANNE S. MILNE, M.B., Ch.B.

Dr. A. S. Milne (neé McNaughton) died in Blackpool on September 9, aged 35.

Anne Sinclair Milne was educated at Glasgow High School and Glasgow University, where, after an outstanding career as a student, she graduated M.B., Ch.B., with honours, in 1947, gaining the Brunton Prize. Later she held resident posts in Ballochmyle Hospital and was eventually medical registrar there. After her marriage in 1950 to Dr. J. Ross Milne she ceased to practise medicine actively, but nevertheless continued to take a keen interest in medical matters, and in fact attended local B.M.A. meetings even after the first major operation of her last illness. She was also actively interested in the affairs of the Medical Women's Federation and was a member of the local committee of the Ladies' Guild of the Royal Medical Benevolent Fund.

A devoted wife and mother of two young daughters, she died at a tragically early age after a long illness. Her passing will be deeply felt by all those who were privileged to be numbered among her friends, and her outstanding courage in the face of an illness, the gravity of which she must have known only too well, will long be remembered.

Medico-Legal

FAILURE OF ACTION IN RESPECT OF GAS-GANGRENE

[From our Legal Correspondent]

On June 29 at Bristol Assizes an action for damages for negligence brought by Mr. Reginald Patch against the Board of Governors of the United Bristol Hospitals was dismissed (*The Times*, June 30).

In 1956 Mr. Patch was suffering from a contracture of the little finger of his right hand, which was also affecting the ring finger. In December of that year he went into hospital for the amputation of his little finger. After the operation gas-gangrene developed, and Mr. Patch's ring finger, and subsequently his middle finger, were removed. Mr. Patch made no complaint of the way in which the operation was performed, but complained that the gas-gangrene developed as a result of overtight bandaging of the hand after the operation and as a result of failure in the post-operative care by doctors and nurses at the hospital. The court found that on the facts there was no evidence of negligence.

The case is not remarkable for the enunciation of any new principle of law, but it is important for the emphatic reminder delivered by Mr. Justice Streatfeild in his judgment that the liability of medical men is not unlimited, and that the standard of care required of them is not that standard shown by exceptional practitioners.

"Surgeons, doctors, and nurses are not insurers. They are not guarantors of absolute safety. They are not liable in law merely because a thing goes wrong. They are not workers of miracles.

"It is as well to remember that the duty of all these professional people is not to have the skill, perception, and knowledge of the topmost specialists in the land, but the law requires them to exercise professionally that skill and knowledge that belongs to the ordinary practitioner."

A doctor must exercise the care of an ordinary reasonable layman. But, in addition, by carrying on practice and holding himself out as a qualified doctor, he becomes bound by a duty not only to use proper care, but also to possess and exercise proper skill. The degree of care and skill required is that which is to be expected of the average practitioner of the class to which the doctor belongs. Greater skill, of course, will be expected of the average specialist than of the average general practitioner.

Spastic's Death after Falls from Bed.—At an inquest in Cardiff on a 9-year-old spastic boy who died after twice falling out of bed in hospital the coroner said that some of the evidence was "disquieting" and that the medical arrangements at the hospital needed tightening up. The boy was stated to have fractured his skull when he fell from bed on the first occasion, and to have opened the fracture and had a fatal haemorrhage on the second occasion. The coroner commented on delays in reporting on the radiograph taken after the first fall and in the medical attention after the second fall. A verdict of accidental death was recorded.—*Manchester Guardian*, August 19.

Universities and Colleges

UNIVERSITY OF OXFORD

The Theodore Williams Scholarship in Anatomy for 1959 has been awarded to Geoffrey Raisman (Pembroke College), and the Theodore Williams Scholarship in Physiology for 1959 to David Keith Parkinson (Christ Church).

UNIVERSITY OF LONDON

The following have been appointed, reappointed, or renominated as representatives of the University on the governing bodies of the institutions indicated in parentheses: Dr. E. R. Cullinan and Dr. J. Forest Smith (Guy's Hospital Medical School); Professor F. R. Goldby (King's College Hospital Medical School); Dr. M. I. A. Hunter and Dr. Katharine G. Lloyd-Williams (Royal Dental Hospital of London School of Dental Surgery); Mr. E. G. Slesinger and Professor J. Z. Young, F.R.S. (St. George's Hospital Medical School); Professor W. C. W. Nixon (St. Mary's Hospital Medical School); Professor R. Hare (Wright-Fleming Institute of St. Mary's Hospital Medical School); Sir Archibald Gray and Sir Charles Harington, F.R.S. (University College Hospital Medical School); Sir Archibald Gray, Dr. C. F. Harris, and Sir James Kilpatrick (British Postgraduate Medical Federation); Professor M. Weatherall (Owen's Schools, Finsbury).

Dr. Macdonald Critchley has been appointed representative of the University at the Darwin Centennial Celebration to be held on November 26, 1959, by the University of Chicago to mark the hundredth anniversary of the publication of Charles Darwin's *Origin of Species*.

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *St. Bartholomew's Hospital Medical College*, Dr. R. I. W. Ballantine, Dr. R. A. Bowen, and Dr. G. H. Ellis (Anaesthetics), and Mr. W. D. Coltart (Orthopaedics). *St. Mary's Hospital Medical School*, Mr. G. L. W. Bonney (Orthopaedics) and Dr. K. A. Porter (Pathology). *Middlesex Hospital Medical School*, Dr. A. C. Boyle (Physical Medicine). *Postgraduate Medical School of London*, Mr. D. G. Melrose (Surgery). *London School of Hygiene and Tropical Medicine*, Dr. W. E. Ormerod (Pathology (Medical Protozoology)) and Dr. B. B. Waddy (Tropical Hygiene). *Institute of Basic Medical Sciences*, Mr. R. J. Last (Anatomy); and Dr. J. B. Walter (probationary recognition for two years from July, 1959, as a teacher of pathology).

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

On July 3 the following candidates were admitted Licentiates in Medicine and Midwifery, having passed the final examinations in medicine, surgery, and midwifery of the Conjoint Board in Ireland:

Adrienne M. Grahame-Ballin, P. J. Breen, S. M. Bridburg, Deirdre M. Burns, J. F. Butler, P. Caplan, M. H. Compion, O. O. Dervish, Bozena H. M. Docherty, D. J. G. Docherty, J. Fernando, D. E. Fitzgerald, Carmin, H. Grange, E. E. Gulland, E. I. Simon-Hart, N. B. Hershfield, M. T. Huxley, E. A. Jangda, D. A. W. Johnson, P. R. Kachan, N. S. Khambalia, K. Kaneshwaran, W. C. Lee, M. Leser, F. E. A. Lesi, J. C. R. Lincoln, J. Y. K. Lip, Anne Llewellin, J. G. Madden, G. S. Mangat, K. T. Mapathe, M. S. Matharu, Y. Minty, Pandora M. Moorhead, C. L. Neimeyer, Jit Seng Ng, P. F. Noone, P. T. Odeghe, H. E. Ofsowitz, Elizabeth C. Ogden, A. Rosenberg, A. E. T. Stewart, P. A. Tan, N. H. Vallani, Constance M. Y. Wong.

COLLEGE OF WILLIAM AND MARY

On June 7 Theodore Bliss, M.B., B.S.(London), graduated from the Wythe-Marshall School of Law, College of William and Mary, Williamsburg, Virginia, U.S.A., with the degree of Bachelor of Civil Law.

Vital Statistics

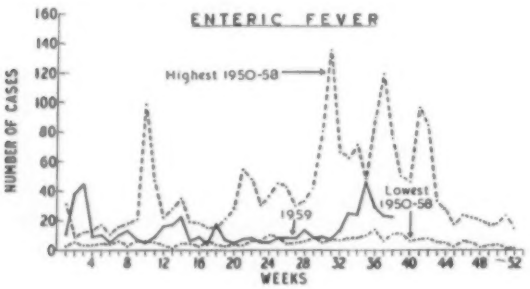
Industrial Accidents and Diseases

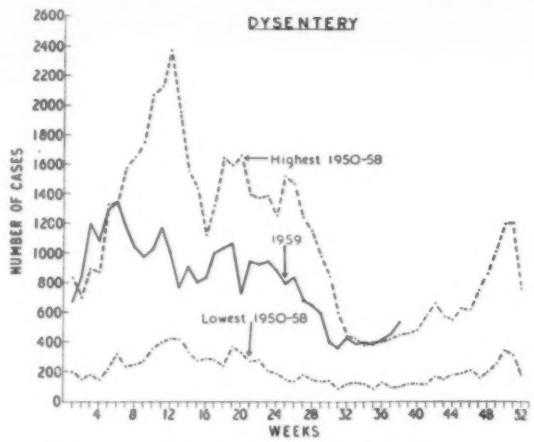
The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in August was 51, compared with 90 in the previous month and 56 in August, 1958.

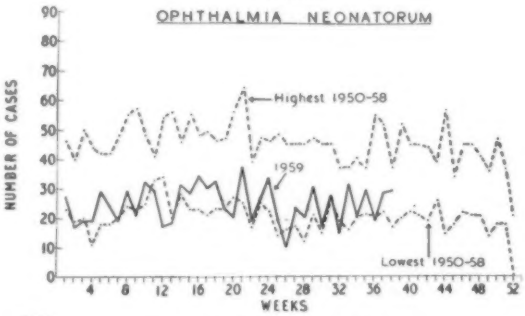
The numbers of cases of industrial diseases in the United Kingdom reported during August were as follows: Lead poisoning 2, mercurial poisoning 1, chronic benzene poisoning 1, compressed air illness 1, epitheliomatous ulceration 23, chrome ulceration 12; total 40. There were 2 deaths from epitheliomatous ulceration due to mineral oil. —*Monthly Bulletin of the Ministry of Health*, September, 1959.

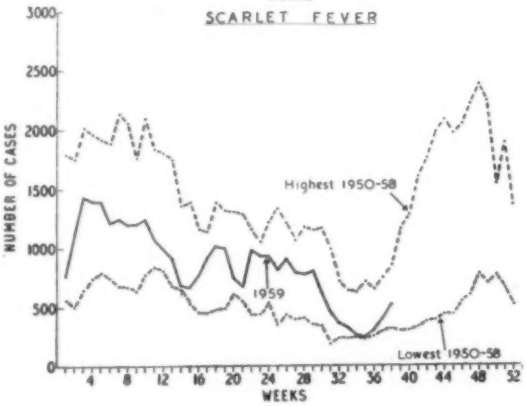
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Scotland in First Quarter

The birth rate for the first quarter of 1959 was 19.9 per 1,000 population, being 0.8 above the average of the five preceding first quarters, and, with the exception of 1947 and 1948, the highest rate in any first quarter since 1928. The infant mortality rate was 33 per 1,000 registered live births, and was 1 above the rate for the preceding March quarter. The stillbirth rate was 22 per 1,000 total births and was the lowest rate recorded in any quarter since registration started in 1939. The neonatal death rate was 22 per 1,000 live births, being 3 above the rate for the first quarter of 1958. The death rate was 16.5 per 1,000 of the population, being 2.2 above the average for the five preceding first quarters, and the highest rate for any quarter since the first quarter of 1951.

Deaths attributed to the principal infectious diseases numbered 525. These were 436 more than in the first quarter of 1958. They included 510 from influenza, 8 from measles, and 7 from meningococcal infections. The 233

deaths from tuberculosis were 4 more than in the preceding first quarter; 218 were attributed to respiratory and 15 to other forms of tuberculosis. Deaths from violence numbered 811, being 65 more than in the first quarter of 1958. 417 of the deaths resulted from accidents in the home, and 129 were due to road accidents.

Week Ending September 26

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Sept. 19	Week Ending Sept. 26
Scarlet Fever		
Warwickshire	9	**31**
Birmingham C.B.	3	**19**
Whooping-cough		
Warwickshire	37	**76**
Birmingham C.B.	19	**40**
Coventry C.B.	12	**29**
Measles		
Lancashire	136	**152**
Atherton U.D.	3	**24**
Acute Poliomyelitis		
London	9	**5**
Sussex	2	**4**
Lancashire	4	**4**
Meningococcal Infections		
Warwickshire	8	**4**
Birmingham C.B.	8	**4**
Continued Fever		
Glasgow	5	**6**
Dysentery		
Hampshire	5	**13**
Southampton C.B.	1	**11**
Lancashire	92	**111**
Liverpool C.B.	37	**22**
Oldham C.B.	0	**11**
Swinton and Pendlebury M.B.	2	**26**
Whiston R.D.	2	**10**
Glasgow	145	**104**
Dundee	28	**33**
Paratyphoid Fever		
Lancashire	4	**6**
Liverpool C.B.	0	**4**
Diphtheria		
London	3	**3**
Finsbury	2	**3**
Food-poisoning		
Suffolk	5	**41**
Ipswich C.B.	3	**41**
Lancashire	97	**85**
Liverpool C.B.	37	**30**
Worsley R.D.	4	**17**
Monmouthshire	0	**18**
Monmouth R.D.	0	**11**
Acute Infectious Encephalitis		
Durham	2	**1**
Gateshead C.B.	2	**1**
Diarrhoea and Enteritis in Infants up to 2 Years		
Dublin County	2	**11**
Dublin C.B.	56	**60**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 19** (No. 37) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	5	3	0	0		3	0	0	0	
Dysentery	449	42	227	7	3	329	54	141	15	14
Encephalitis, acute	10	1		1		2	1		0	
Enteric fever:										
Typhoid	9	2	1	1	1	2	0	0	1	
Paratyphoid	14	0	0	0	4(B)	4	0	4(B)	0	4(B)
Food-poisoning	293	29	32	6		302	55	21	2	
Infective enteritis or diarrhoea under 2 years				21	62				11	67
Measles*	686	29	8	43	63	1,603	94	20	12	34
Meningococcal infection	20	3	7	2		16	2	9	1	
Ophthalmia neonatorum	28	6	6	0		48	7	4	0	
Pneumonia†	132	12	103	3		145	12	127	1	1
Poliomyelitis, acute:										
Paralytic	19	8	0	1	3	40	1	16	0	9
Non-paralytic	14	1	3			22	0			
Puerperal fever§	215	28	15	0		206	33	6	0	
Scarlet fever	402	32	84	19	20	296	30	66	10	28
Tuberculosis:										
Respiratory	366	34	57	9		500	71	90	31	
Non-respiratory	59	3	15	3		69	5	19	2	
Whooping-cough	718	32	131	7	50	746	38	115	56	24

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	0	0	0		1	0	0	0	0	0
Dysentery	0	0		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	7	0	0	0	0	4	0	0	0	1
Influenza	1	0	0	0	0	2	0	0	0	0
Measles		0	0	0			0	0	0	
Meningococcal infection		0	0				0	0		
Pneumonia	265	18	14	5	3	273	14	7	10	11
Poliomyelitis, acute	2	1		0	0	4	0	1	0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	61	2	8	1	6	67	6	3	0	
Non-respiratory		2	1	0	0		0	0	0	
Whooping-cough	1	0	1	0	0	1	0	0	0	0
Deaths 0–1 year	257	23	19	6	9	281	26	29	4	22
Deaths (excluding stillbirths)	7,643	613	463	99	124	7,759	614	467	89	151
LIVE BIRTHS	13,740	1210	895	261	395	13,702	1159	918	197	324
STILLBIRTHS	273	24	24			298	22	15		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Epsom Scholarships.—The council of Epsom College will, early in June, 1960, award two or more "Henry Robinson" Scholarships on the results of competitive examination.

Candidates must be the sons of registered medical practitioners, and aged under 14 but not less than 12 on January 1, 1960. The scholarships are tenable, subject to good conduct, for the whole of the school careers of those elected. The normal maximum value is £250 per annum for a boarder and £150 for a day boy; but the council have a discretion to exceed these amounts for a boy of unusual brilliance. The total annual value to be awarded in 1960 is not less than £425, and there is no means test for these scholarships. Candidates are eligible also for the Open College Scholarships, of which there are six each year ranging in amount up to £150 (boarders) and £50 to £100 (day boys); for these they compete on equal terms with sons of non-medical parents.

Full particulars may be had from the Headmaster at the College, Epsom.

Care of Airborne Monkeys.—The British Standards Institution has published recommendations giving guidance to airlines on the handling of rhesus and other small monkeys intended for laboratory use. Apart from dealing with the actual care of the monkeys, this standard (B.S.3149. Part 1) is also concerned with the health of the animal-handlers, and recommends that they produce evidence of fitness, including freedom from active tuberculosis. An approved list of animal-handlers, and of agents of importing firms, is being prepared. These recommendations, based on background work carried out by the Medical Research Council, will be followed by others dealing with various mammals, birds, fish, reptiles, and invertebrates. In January this year about 200 (25%) of a consignment of monkeys being flown from Ethiopia to Canada were found to have died from gastro-enteritis when the plane touched down at London. Last week nearly half of a consignment of 300 rhesus monkeys from Singapore died before the British vessel *Benlomond* reached the West India Docks.

Middlesex Hospital Medical School.—The annual dinner for past and present students at the Savoy Hotel on October 2 was a pleasantly domestic occasion. Some 350 people attended it. The chairman was Professor J. H. Woodger, who has just retired as head of the department of biology at the school after 37 years—"Young Woodger," as Sir Charles Dodds was pleased to call him, speaking, so he claimed, from his vantage point as senior of London University's 421 professors. (Sir Charles was appointed to his chair in 1925.) Details were given at the dinner of both progress and setbacks in the school's building programme, and new evidence of the successful invasion of medicine by women was provided by the senior Broderip scholar, who this year, for the first time, was a woman, Miss Barbara Lockley. Learned (Newnham Scholar and double first) yet elegant, Miss Lockley gave a capital and spirited reply, after the Dean, to the toast of the Medical School and Hospital. Her speech in its brevity and wit was a model to her elders. The Dean, Professor B. W. Windeyer, announced that Phase I of the rebuilding of the School would be finished in six weeks and opened in December. But there was a shortage of £500,000 for the remainder. The School and its benefactors had raised £750,000 and the University Grants Committee has provided £500,000, enough together for the purchase of the site and for Phases I, III (the Astor Residential College), and part of Phase II. The rest of Phase II would have to await further funds. Among the guests were Lord Astor of Hever, Sir Harry Jephcott, and the Mayor of St. Marylebone.

Apothecaries' New Faculty.—A Faculty of the History of Medicine and Pharmacy was founded recently under the auspices of the Worshipful Society of Apothecaries of London, which received its charter in 1617. Its aim is to foster interest in medical history, and to attract the co-operation of general historians so that work in this field may be co-ordinated with wider historical studies. It will provide in its ancient Hall a central meeting-point for historians and medical and pharmaceutical historical societies. A research fellowship, generously endowed by the Wellcome Trustees, is held at present by Mr. R. S. Roberts, a professional historian, who is working upon the early organization of the drug trade from the sixteenth century. The foundation members of the Faculty are: Sir John Charles, Sir Zachary Cope, Dr. W. S. C. Copeman (*chairman*), Dr. Macdonald Critchley, Sir Charles Dodds, F.R.S., Professor J. G. Edwards, Professor John Fulton (Yale, U.S.A.), Dr. F. H. K. Green, Dr. Douglas Guthrie, Sir Hugh Lett, Sir Arthur MacNalty, Dr. W. H. McMenemey, Professor Douglas McKie, Sir Robert Platt, Dr. F. N. Poynter, Dr. H. M. Sinclair, Professor Charles Singer, Dr. R. R. Trail, Sir Cecil Wakeley, Mr. A. Dickson Wright, and the Master and Wardens of the Society of Apothecaries (*ex officio*). Inquiries should be sent to Ernest Busby, Esq., Clerk to the Worshipful Society of Apothecaries, Blackfriars Lane, London, E.C.4.

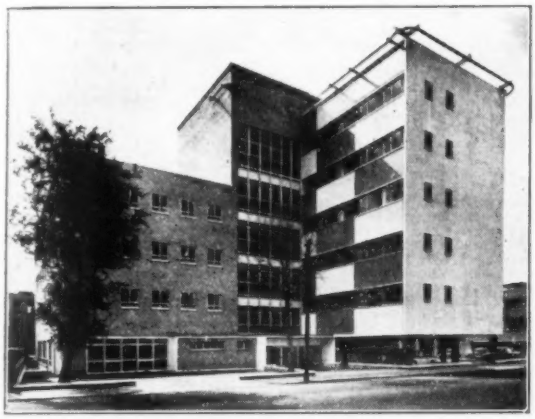
Czechoslovakian Psychiatric Congress.—An international psychiatric congress was held at Jesenik, in Czechoslovakia, from September 9 to 11. The generous hospitality of the Czech hosts was exemplary and every effort was made to accommodate visitors from 18 nations. To the small number of participants from Western countries, including four from the United Kingdom, the meeting provided an opportunity for a close look at psychiatry behind the Iron Curtain. The main theme of the congress was "Neurosis," a topic which is peculiarly well suited to controversy and speculation in the absence of much factual information. Few doubts, however, appeared to assail the 21 Russian delegates, who were the pacemakers of the occasion. Their positive views of human behaviour were squarely based on a combination of Pavlovian physiology and Marxist dogma. Their negative views were clearly expounded by Professor F. V. Bassin, of Moscow, in a paper entitled "The Ideological Struggle with Neo-Freudism." The cautious agnosticism of Western psychiatry as a whole was given less vociferous expression than the forthright defence of psycho-analysis expounded by some individual delegates, but friendly and often informative psycho-political discussions continued in and out of the congress hall throughout the meetings. It is to be hoped that the debate may be resumed on a future occasion.

Scottish Society of Physicians.—The first meeting of the Scottish Society of Physicians was held at Glasgow University on September 25 and 26. The Society's objects are "to encourage the study and discussion of clinical, scientific, and medical work; and to promote friendship and social contact between physicians practising in Scotland." The present membership is 143. The Society plans to meet yearly, visiting teaching and non-teaching centres in rotation. At the inaugural meeting a constitution was adopted, scientific papers were read and discussed, and a dinner was held in the Hall of the Royal Faculty of Physicians and Surgeons. The following were elected office-bearers for the ensuing year: *president*, Dr. A. A. F. Peel (Glasgow); *president-elect*, Dr. J. Ronald (Inverness); *secretary*, Dr. T. Semple (Glasgow); *treasurer*, Dr. R. Marquis (Edinburgh); *committee*, Dr. K. N. V. Palmer (Aberdeen), Dr. J. Laurie (Dumfries), Dr. K. G. Lowe (Dundee), Dr. J. D. Buchanan (Dunfermline), Dr. R. Turner (Edinburgh), Professor K. W. Donald (Edinburgh), Dr. J. A. W. McCluskie (Glasgow), and Dr. I. Easton (Perth).

Seed Memorial Prize.—The North of England Otolaryngological Society announces that the George Seed Memorial Prize (previously known as the "Fifty Guinea Prize") will be awarded in 1960 for an original paper on work in otolaryngology carried out in the North of England. The investigation must have been carried out during the tenure of a post of senior registrar, house officer, registrar, or clinical assistant. Entries (3 copies) should be

sent, before August 31, 1960, to the Honorary Secretary, North of England Otolaryngological Society, 38, Huddersfield Road, Barnsley, Yorks.

Boots Research Centre.—A new research centre costing £750,000 was opened in Nottingham on September 22 by Boots Pure Drug Co. Ltd. The 24 laboratories shown here will provide facilities for research in pharmacology and



chemotherapy, and for analytical and control work in the bio-assay and microbiology divisions of the company's standards department. The building also houses a scientific library of 25,000 volumes, a lecture theatre seating 200, and a radioactive isotope unit.

Coventry Blood Donors' Association Award.—The Coventry and District Voluntary Blood Donors' Association is to make an award of £25 each year to a person judged to have made an outstanding contribution to the knowledge of blood transfusion or the science of haematology. The award is open to any person of any age or nationality for work done in Great Britain. Applications, or nominations, should be sent to the Association's Hon. General Secretary, Mr. L. G GRIESBACH, 6, Delhi Avenue, Coventry, Warwickshire, before December 31.

Epilepsy in Children.—The World Health Organization Study Group on Juvenile Epilepsy that met in London in 1954 held a second informal meeting at Stora Skondal in Stockholm during August, to review the progress made in the care of epileptic children during the last five years. Dr. KARL-AXEL MELIN, director of the epileptic clinic at Stora Skondal, was the host, and specialists from most of the West European countries attended. It is hoped that a report of the proceedings will be published as a W.H.O. bulletin.

Director of Greenwich Hospital.—Mr. H. D. SAMUEL, who is Under-Secretary at the Admiralty, has been appointed to succeed Mr. R. MILLAR as director of Greenwich Hospital from October 1.

King's Dinner.—For the first time in its history, this year's annual dinner of the King's College Hospital Medical School, held at the Savoy Hotel on October 3, was presided over by one of the school's distinguished daughters, Dr. CICELY D. WILLIAMS. She delighted her audience with a brisk summary of some of the events, grave and gay, in her 30 years' pioneer work for mothers and children in no fewer than 38 countries. Included in this period was three years spent in a Japanese prison camp, but even of this Dr. Williams had something amusing to say. In a serious vein she pleaded that medicine in this country should take more interest in the medical needs of developing countries, especially in respect of training programmes and post-graduate courses. Continuity of service mattered. The problems of working among backward people could not be mastered in a short time, and the effectiveness of the medical services depended on the personality of the doctor, accuracy of observation, and adaptation to needs and resources rather than the availability of laboratories and statistics. Dr. Williams instanced how sometimes 250 out-patients had to be dealt with in a day, frequently with the aid of interpreters. Often a reply bore no relation to a simple question after each had travelled to and fro. The answer, for example, to the question, "How long has your child been ill?" might well come back in due course as, "Yes."

Withdrawal of Arsenic Crop Spray.—Fisons, the agricultural fertilizer manufacturers, have announced that they will no longer produce or distribute any arsenical weed-killer or defoliant. Supplies already issued to distributors will be withdrawn. (*The Times*, October 6.)

COMING EVENTS

Institute of Psychiatry.—Public lecture by Sir RUDOLPH PETERS, F.R.S., on "Convulsive Conditions and Enzyme Biochemistry." November 26, 5 p.m., at the Maudsley Hospital, Denmark Hill, S.E.5.

London Medical Exhibition.—New Hall, Royal Horticultural Society (off Vincent Square), London, S.W.1, November 16–20. Times of opening: 11 a.m.–6.30 p.m.; Thursday, November 19, to 7.30 p.m. Details from the Exhibition, 194–200, Bishopsgate, London, E.C.2 (Ave 1444).

British Occupational Hygiene Society.—The 11th Conference will discuss problems of heating and ventilation as they affect personnel working in arduous environments. November 4, Institute of Mechanical Engineers, Westminster, London. Non-members may attend on payment of a registration fee. Details from Dr. D. TURNER, Associated Ethyl Company, Ltd., Ellesmere Port, Cheshire.

Symposium on Inhaled Particles and Vapours, Oxford, April, 1960. Details from Dr. J. S. MCLINTOCK, National Coal Board, Hobart House, London, S.W.1.

Meeting of International Organization Against Trachoma.—Athens, April 20, 1960. Details from Dr. J. SEDEN, 94, Rue Sylvabelle, Marseilles, France.

2nd Venezuelan Congress of Obstetrics and Gynaecology.—Caracas, February 19–24, 1960. Details from Dr. H. MARCANO GUZMAN, Sociedád de Obstetricia y Ginecología de Venezuela, Maternidad "Concepción Palacios," Caracas.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Medical and Biological Illustration.—Issued quarterly (£3 annually). The new issue (Vol. 9, No. 3) includes:

FRONTISPIECE.
NECTAR SECRETION IN THE FLOWER OF THE IVY. Douglas F. Lawson.
JOHN HUNTER'S ARTISTS. Jessie Dobson.
DIRECT ULTRA-VIOLET PHOTOGRAPHY OF THE SKIN. Raymond J. Lunnon.
SOME OBSERVATIONS ON KINEMATOGRAPHY IN OPHTHALMIC SURGERY. Robert A. Leonard.
A METHOD OF STUDYING MUSCULAR ACTIVITY DURING WALKING. R. H. Hardy.
A TIME-LAPSE UNIT FOR TISSUE CULTURE RESEARCH. J. D. Biggers, A. R. Michaelis, John Gunner, and John Roberts.
NEW DESIGN AND TEACHING FACILITIES IN THE ANATOMY DISSECTING ROOM. C. A. Erskine.
EQUIPMENT AND METHODS:
THE HULCHER 70 SEQUENCE CAMERA.
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SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 12

LONDON UNIVERSITY.—(1) At Senate House, W.C., 5.30 p.m., special university lecture in dietetics by Dr. E. G. Holmes (East Africa): Aspects of Human Body Composition Related to Diet and to Some Endocrine Factors. (2) At Anatomy Lecture Theatre, University College, W.C., 5.30 p.m., special university lecture in the history and philosophy of science by Professor C. D. O'Malley (California): Andreas Vesalius—The Development of a Scientist—(i) The Student: Paris and Louvain.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—4 p.m., Benzué Memorial Award Lecture by Dr. Denis Hill: Role of Psychiatry in Medicine.

ROYAL SOCIETY OF MEDICINE.—In Barnes Hall, 2.30 p.m., 1st Nuffield Lecture by Sir Clement Price Thomas.

Tuesday, October 13

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—At 36, Harborne Road, Edgbaston, 8 p.m., Dr. C. W. Gordon: Hospital Facilities for Psychiatry in the Birmingham Region.

BRITISH ASSOCIATION OF SPORT AND MEDICINE.—At Arthur Stanley Institute, Peto Place, Marylebone Road, London, N.W., 5 p.m., Dr. J. M. Tanner and Dr. J. Fletcher: Results of Individual Research at the Empire Games.

FOUNTAIN HOSPITAL.—5.30 p.m., subject: Community Care of the Mentally Subnormal and the New Mental Health Act. Dr. D. H. H. Thomas: Hospital's Role in the Future Service; Dr. G. S. Wigley: Local Health Authority and the Future Service.

HEATHERWOOD ORTHOPAEDIC HOSPITAL.—8.30 p.m., Mr. J. P. Jackson: Joint Fusion in Children.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-60.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. J. M. Roberts: Use and Abuse of Tranquillizers.

LEEDS UNIVERSITY: FACULTY OF MEDICINE.—At Riley Smith Hall, University Union, 3 p.m., Inaugural Lecture by Mr. Norman Fisher, M.A.: Culture and Allergy.

MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Staff House, Manchester University, 7.45 for 8 p.m., Presidential Address by Mr. I. M. Orr: Surgical Problems of the Upper and Lower Extremities of the Oesophagus.

Wednesday, October 14

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. Tickner: The Biochemistry of Exfoliative Dermatitis.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. D. T. Carr: Pleural Fluid Glucose: with Particular Reference to Effusions in Rheumatoid Arthritis.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. H. Harkness: Non-gonococcal Urethritis.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital Medical School, 8.30 p.m., Dr. Patricia Shaw, Dr. Marjory Warren, and Mr. D. C. R. Munro: Problems of Old Age.

LONDON UNIVERSITY.—At Anatomy Lecture Theatre, University College, W.C., 5.30 p.m., special university lecture in the history and philosophy of science by Professor C. D. O'Malley (California): Andreas Vesalius—The Development of a Scientist—(ii) The Teacher: Padua and Bologna.

MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Large Anatomy Theatre, Medical School, Manchester University, 4.30 for 5 p.m., Dr. P. J. L. Sequeira: Serology of Venereal Diseases.

PHARMACEUTICAL SOCIETY OF GREAT BRITAIN.—7.30 p.m., Dr. A. M. Cook, B.Pharm., Ph.D.: Evaluation of Disinfectants and Preservatives.

Thursday, October 15

LONDON UNIVERSITY.—(1) At Anatomy Theatre, Gower Street, W.C., 1.15 p.m. Dr. H. Kalmus: Sensations and Stimuli. (2) At Senate House, W.C., 5.30 p.m., special university lecture in dietetics by Dr. E. G. Holmes (East Africa): Aspects of Human Body Composition Related to Diet and to Some Endocrine Factors. (3) At Anatomy Lecture Theatre, University College, W.C., 5.30 p.m., special university lecture in the history and philosophy of science by Professor C. D. O'Malley (California): Andreas Vesalius—The Development of a Scientist—(iii) The Fabrica.

MANCHESTER MEDICAL SOCIETY: SECTION OF ANAESTHETICS.—At Staff House, Manchester University, 7.45 for 8 p.m., Presidential Address by Dr. E. F. Hill: 50 Years of Anaesthesia.

NUFFIELD ORTHOPAEDIC CENTRE.—At Winsfield-Morris Orthopaedic Hospital, 8.30 p.m., Professor C. Casuccio: Some Observations on the So-called "Senile" Osteoporosis.

ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Normal Vision and "Refraction Patients."

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At 26, Portland Place, 7.30 p.m., Presidential Address by Sir William MacArthur: Identification of Some Pestilences of the Past.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Denis Williams: demonstration in neurology.

Friday, October 16

FACULTY OF RADIOLOGISTS.—At University College Hospital Medical School, 4.30 p.m., Professor M. Rosenheim and Dr. C. J. Hodson: Radiology in Hypertension of Renal Origin.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. F. R. Bettley: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. Lloyd Rusby: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. A. S. Walker: Management of Deaf Children.

INSTITUTE OF NEUROLOGY.—4.45 p.m., Dr. R. T. C. Pratt: Genetics.

KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.

LONDON UNIVERSITY.—At Senate House, W.C., 5.30 p.m., special university lecture in dietetics by Dr. E. G. Holmes (East Africa): Aspects of Human Body Composition Related to Diet and to Some Endocrine Factors.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES.—At County Hall, S.E., (1) 1.15 p.m., 38th annual general meeting; (2) 2.30 p.m., general meeting in conjunction with the General Assembly of the International Union Against the Venereal Diseases and the Treponematosis.

PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., short papers by Mr. D. A. Barley, Dr. M. E. Gordon, Dr. H. Greenburgh, and Dr. R. Simpson-White.

SOCIETY OF CHEMICAL INDUSTRY: FINE CHEMICALS GROUP.—At Westminster Medical School, 6.30 p.m., Professor J. N. Davidson: Chemistry and Biochemistry of the Nucleic Acids.

Saturday, October 17

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 10 a.m., Dr. I. Yentis: Radiodiagnosis; 10.30 a.m., Dr. J. F. Bromley: Radiotherapy; 11.30 a.m., Dr. R. C. S. Pointon: Chemotherapy.

NORTH-EAST METROPOLITAN THORACIC SOCIETY.—At Broomfield Hospital, near Chelmsford, Essex, 10.30 for 11 a.m., joint meeting with East Anglian Thoracic Society. Dr. M. Barry: Experience in Finding Congenital Heart Disease from Chest X-rays; Mr. Geoffrey Flavel: The Treatment of Hiatus Hernia; Mr. B. B. Millstein: Atrial Septal Defects; Dr. E. G. Sita-Lumsden: Chronic Berylliosis.

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.—At Liverpool, 2 p.m., 13th Annual and 37th Ordinary Meeting.

Sunday, October 18

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—10.15 a.m., seminar for general practitioners. Mr. Anthony Radcliffe: Common Ear, Nose, and Throat Conditions.

MANCHESTER UNIVERSITY: FACULTY OF MEDICINE AND COLLEGE OF GENERAL PRACTITIONERS: NORTH-WEST ENGLAND FACULTY.—At Theatre 1, Clinical Sciences Building, York Place, 11 a.m., Dr. W. Brockbank, Mr. J. B. Lloyd, and Dr. Basil Lee: Cost of Prescribing.

APPOINTMENTS

EVANS, R. G., M.B., B.Ch., D.P.H., C.P.H., County Medical Officer of Health for Breconshire.

HOSPITALS FOR DISEASES OF THE CHEST.—J. C. W. MacFarlane, M.D., Whole-time Clinical Pathologist, London Chest Hospital; M. Paneth, B.M., B.Ch., F.R.C.S., Part-time Consultant Thoracic Surgeon, Brompton Hospital.

MANCHESTER REGIONAL HOSPITAL BOARD.—R. M. Winston, M.D., Whole-time Clinical Pathologist, Hope Hospital, Salford; Eleanor B. Schill, M.B., Ch.B., D.P.M., Assistant Psychiatrist (S.H.M.O.), two half-days weekly, Withington Hospital, Manchester; W. M. S. Kelso, M.B., Ch.B., F.R.C.S.Ed., Whole-time Senior Casualty Officer, Preston Royal Infirmary; R. H. Martin, M.B., Ch.B., F.R.C.S.Ed., M.R.C.O.G., Consultant Obstetrician/Gynaecologist (eight half-days weekly), South Manchester Hospitals; S. L. Pugmire, L.R.C.P.&S.I., Whole-time Assistant Psychiatrist (S.H.M.O.), Whittingham Hospital, near Preston; C. C. Moir, M.B., Ch.B., Whole-time Assistant Pathologist (S.H.M.O.), Preston and Chorley Hospitals; A. St. J. Wilding, M.B., Ch.B., Whole-time Assistant Pathologist (S.H.M.O.), Ashton, Hyde, and Glossop Hospitals; J. C. Denmark, M.B., Ch.B., D.P.M., Whole-time Assistant Psychiatrist (S.H.M.O.), Lancaster Moor Hospital; W. J. Atkinson, M.D., M.S., F.R.C.S., Maximum Part-time Consultant Neurosurgeon, Crumpsall, Booth Hall and Prestwich Hospitals; W. H. Lonsdale, M.B., Ch.B., F.R.C.S., Consultant Surgeon (eight half-days weekly), Preston and Chorley Group of Hospitals; R. D. Young, M.D., M.R.C.P.Ed., Consultant Chest Physician (seven half-days weekly), Lancaster and Kendal Hospitals; A. H. Barber, M.B., Ch.B., F.R.C.S., M.R.C.P., Consultant Obstetrician Gynaecologist, Oldham and District Group of Hospitals (eight half-days weekly); P. C. Leeson, M.B., B.S., F.R.C.S., D.L.O., Consultant Ear, Nose, and Throat Surgeon to Salford and West Manchester Groups of Hospitals (maximum part-time); R. L. Gadd, M.B., Ch.B., F.R.C.S.Ed., M.R.C.O.G., Consultant Obstetrician Gynaecologist to Ashton, Hyde, and Glossop Group of Hospitals (maximum part-time); A. D. Clarke, M.B., Ch.B., F.F.A. R.C.S., D.A., Consultant Anaesthetist, South Manchester Group of Hospitals (nine half-days weekly); J. A. M. Smith, M.D., M.R.C.O.G., Consultant Obstetrician Gynaecologist to Burnley and District Group of Hospitals (eight half-days weekly); D. Longson, M.B., Ch.B., M.R.C.P., Consultant Endocrinologist, United Manchester Hospitals, Booth Hall Hospital, and Royal Manchester Children's Hospital (maximum part-time) (joint appointment with Board of Governors of United Manchester Hospitals).

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Benwell.—On September 28, 1959, at North Walsham Hospital, Norfolk, to Jean (formerly Crist), R.S.C.N., wife of John Benwell, M.B., B.S., D.C.H., a daughter—Elizabeth Helen.

DEATHS

Ainsworth.—On September 5, 1959, at his home, Lytham House, Kirkley, near Liverpool, Richard Ainsworth, M.B., aged 87.

Becket.—On August 28, 1959, at 187, Park Lane, Macclesfield, Cheshire, Jeremiah Christopher Becket, M.B., B.Ch., formerly of Ebbw Vale, Mon., aged 39.

Bennett.—On September 9, 1959, at 19A, King Edward Parade, Devonport, Auckland, New Zealand, Francis Lionel Percy Garnet Bennett, M.C., M.B., B.Ch., late of Glandore, St. Mary's, Isles of Scilly, aged 70.

Campbell.—On September 11, 1959, at Glen Tachur Hotel, Pinwherry, Ayrshire, John Campbell, M.C., M.B., Ch.B., of Chipstead House, Birtley, Co Durham.

Currie.—On September 11, 1959, at Edinburgh City Hospital, James Grant Currie, L.R.C.P.&S.Ed., L.R.F.P.S., Surgeon Commander, R.N., retired, of 5, Rothesay Terrace, Edinburgh.

Davis.—On September 9, 1959, at Greenbank Hospital, Plymouth, Devon, William Herbert Davis, M.R.C.S., L.R.C.P., of 23, Church Street, Woodbury, Devon, aged 85.

Durnin.—On September 3, 1959, at 83, Morley Road, Chaddesden, Derby, Charles Durnin, M.B., B.Ch., aged 59.

Edmonds.—On September 1, 1959, Mary Therese Edmonds, M.B., B.S., of 18, Giggs Hill Gardens, Thames Ditton, Surrey.

Macaskie.—On September 7, 1959, at Melbourne, Australia, Frank Bertram Macaskie, L.R.C.P.&S.Ed., L.R.F.P.S., late of Seahouses, Northumberland.

McKibbin.—On September 10, 1959, at his home, Lierre, Daleside Gardens, Chigwell, Essex, Noble McKibbin, M.B., B.Ch.

Milne.—On September 9, 1959, at Blackpool, Lancs, Anne Sinclair Milne (formerly McNaughton), M.B., Ch.B., aged 35.

Miskin.—On September 5, 1959, in a nursing-home, Hove, Sussex, Ernest Miskin, M.B., of 101, Holland Road, Hove, aged 89.

Mitchell.—On September 2, 1959, at Edinburgh, Alexander Philip Mitchell, M.D.Ed., Ch.M., F.R.C.S.Ed.

Steel.—On September 6, 1959, at Victoria, British Columbia, Canada, the result of a riding accident in May, 1956, Anne Margaret Steel, M.B., Ch.B., aged 39.

Waller.—On September 1, 1959, Arthur Beaumont Waller, M.B., of Ellenslea, Station Street, Kirkby-in-Ashfield, Notts.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Cortisone and Response to Immunization

Q.—*Is the production of antibodies in diphtheria, pertussis, tetanus, poliomyelitis, and B.C.G. vaccinations modified by long-term treatment with cortisone? Are there any special precautions to be taken in undertaking any of these immunization procedures in children already receiving cortisone as long-term therapy?*

A.—Prolonged cortisone therapy may interfere with immunity responses. This is best illustrated by the severe, sometimes fatal, forms which a disease like chicken-pox may assume in a child on prolonged cortisone treatment—presumably due to failure of immune mechanisms following infection. Similar failure might follow artificial stimulation of the immune mechanisms by immunization procedures, but the only way to test this in a child would be by antibody titration after immunization. Diphtheria, pertussis, tetanus, and poliomyelitis immunizations are carried out with dead vaccines or toxoids, and no special precautions are necessary—cortisone would in fact tend to damp down any reaction. B.C.G. vaccine, on the other hand, is a live vaccine, and prolonged cortisone therapy might, as in chicken-pox, interfere with immune responses and lead to serious reactions or even generalized disease. Unless danger of exposure to tuberculosis was a serious risk it would be safer not to give this vaccine, but if regarded as essential then one should be prepared to treat with antituberculous drugs any sign of dissemination. This question emphasizes the risk that children on prolonged cortisone treatment run from normally simple infections. A hospital ward, with constant risk of infection, is not the best place for them. It has been suggested that where the risk of infection is high repeated doses of gamma-globulin might be desirable for children on prolonged cortisone therapy.

Ultrasonic Therapy for Multiple Sclerosis

Q.—*What effect does treatment with ultrasonics have on multiple sclerosis?*

A.—A focal destructive lesion in the nervous system can be produced by ultrasonic waves, and as a method of treatment this has possible applications in the stereotaxic cerebral surgery of involuntary movements or in the production of closed leucotomy and similar operations. The destructive nature of the lesion must, however, be stressed, and, apart from a possible secondary interference with the pathological mechanisms involved in the disease, it seems unlikely to have any specific effect in multiple sclerosis or any general applicability to this disease.

Battery-operated Photoelectric Haemoglobinometer

Q.—*Is a battery-operated photoelectric haemoglobinometer obtainable? In our mission hospital in Africa we have electricity only at night.*

A.—The M.R.C. photometer is the best visual haemoglobinometer so far available. It is calibrated by the National Physical Laboratory and rarely, if ever, requires recalibration. It is usually supplied to work off the 230/250-volt mains, but uses "Pigmy Sign, S.B.C. 2 contact" bulbs, 28 mm. in diameter and 62 mm. long overall, which are also available for voltages of 25, 35, 50, 55, 60, 65, 75, 150, 100/110, 120/130, 200/220, 230/250. Two 12-volt car batteries in series would supply the lowest of these voltages.

If none of these are suitable, a motor-car "stop and tail" lamp for 6 or 12 volts with an S.B.C. cap might be suitable, but the electric circuit would need some modification, since the common lead is connected to the external cap. These lamps require 21 or 6 watts. However, the M.R.C. photometer is designed so that it can be used by either daylight or electrical illumination, so perhaps the simplest solution would be to unscrew the electrical illuminating attachment and point the instrument out of a north window.

Culturing Malignant Cells

Q.—*What culture media are used for culturing malignant cells?*

A.—The media used for the growth of malignant cells *in vitro* are in general the same as those used for their normal counterparts. In its simplest form the medium consists of a chick-plasma-clot substratum with the addition of serum (not necessarily from the same species)[1] and an extract of embryonic tissue (usually chick) in a balanced salt solution (such as, for instance, Tyrode's). It was early noted[2] that tumour cells tended to liquefy the plasma clot and were less fastidious in their requirements, although by no means all tumour material is easy to grow. Culture media vary from the simple plasma-serum-embryo extract mentioned above to the complex synthetic and semi-synthetic media dating from that of Fischer. These include the highly complex media of Morgan, Morton, and Parker No. 199 and that of Parker and Healy No. 858 and the somewhat simpler medium MB.752/1 of Waymouth. These culture media are described by Paul.[3]

Cells undergo "alteration" and become less fastidious or more vigorous in long-term culture, and it is interesting to note that not only can normal cells become malignant in culture[4] (with or without a carcinogen), but tumour cells may lose their malignant properties[5]—and it is suggested that only in a purely synthetic medium, in which growth is poor, can a stable line be maintained.

References

1. Fischer, A., and Davidsohn, F., *Nature*, 1939, **143**, 436.
2. Carrel, A., and Burrows, M. T., *J. exp. Med.*, 1911, **13**, 571.
3. Paul, J., *Cell and Tissue Culture*, 1959, Livingstone.
4. Earle, W. R., *J. nat. cancer Inst.*, 1943, **4**, 131.
5. DeBruyn, H., and Gey, E., *International Union of Cancer Paris Acta*, 1951, **7**, 772.

Metabolic Response to Childbirth

Q.—*Is there a metabolic response to childbirth analogous to the metabolic response to surgery?*

A.—Adrenal hyperplasia and overactivity is a feature of normal pregnancy and is presumably responsible for, or contributes to, the salt retention which is known to occur. There is therefore an adrenal metabolic response to pregnancy, but it is abruptly terminated after delivery. Any complicated delivery, however, must be regarded as a surgical operation, and there is no reason to suppose that the body's response to intervention by the obstetrician differs from its response to other surgical procedures. It must be borne in mind that much of the so-called metabolic response to surgery—which includes negative nitrogen-balance and salt depletion—has been shown to be the result of the deprivation of food and fluid which inevitably accompanies surgical treatment.

Pre-employment X-ray of Spine

Q.—*Is there any value in routine x-ray examination of the lumbar spine and sacro-iliac joints in pre-employment medical examinations of candidates for employment in heavy work?*

A.—The incidence of congenital anomalies in the lumbar spine is very high. Some of these reduce the mobility of the lumbo-sacral disk and are thought to throw a heavier strain on the remaining mobile disks, thus predisposing to disk trouble. The evidence for this is doubtful, and it would not be advisable to refuse employment for heavy work on the basis of such findings.

Pathological disk narrowing, buttressing, and evidence of old disk degeneration do tend to be found in patients subject to backache. However, not all patients with

abnormal changes such as these have backache on heavy work, and in many patients with backache the *x*-ray findings are normal. Therefore it is very doubtful whether pre-employment *x*-ray examinations would be worth while, though evidence gained from them might have some bearing in medico-legal decisions on the responsibility for backache after specific injury. *X*-ray examination of the sacro-iliac joints would be useful only in discovering ankylosing spondylitis, and this is uncommon enough to make special examination not worth while.

Sweats after Infective Hepatitis

Q.—*A man aged 56 who is convalescing from infective hepatitis has one or more profuse sweats (limited to head, neck, and upper trunk) in the early hours of each morning. Why should this be?*

A.—It is doubtful if these sweats are of any serious significance, though most unpleasant. It is not possible to explain their mechanism more than to say that they may occur during convalescence from any infective, and particularly viral, illness. Presumably they represent a temporary disturbance of heat-regulating mechanisms. I assume that there is no fever and that the original diagnosis is not in doubt. If symptoms continue it might be worth considering other causes, particularly a stone in the common bile duct. Other possibilities are infectious mononucleosis (glandular fever), one of the reticuloses, and collagen disease: these, however, are of little practical importance compared with gallstones, which may closely mimic infective hepatitis if pain is absent.

Cruelty to Children

Q.—*Under what circumstances may a doctor called in by the N.S.P.C.C. issue a certificate for the removal of children from their home to a place of safety? What medical and social conditions constitute "unnecessary suffering"?*

A.—A doctor does not issue a certificate for the removal of a child from its home to a place of safety; but the person seeking to remove the child (a constable or any person—e.g., an N.S.P.C.C. officer—authorized by any court or by any justice of the peace) usually seeks a doctor's certificate as supporting evidence. The doctor issuing such a certificate must be prepared to appear in court to substantiate, with factual evidence, the need for the removal of the child. This may involve subjection to cross-examination.

There cannot be a precise definition of what constitutes unnecessary suffering. In addition to malnutrition and inadequate clothing, deliberate omission to supply medical and surgical aid could be held to cause unnecessary suffering. Moral and religious welfare must be considered as well as physical well-being. Mental as opposed to physical suffering must also be borne in mind. The circumstances in which a child may be removed to a place of safety are enumerated in the Children and Young Persons Act, 1933 (Section 67, the first schedule of the Act).

Mastoid Operation and Damage to Eardrum

Q.—*Is the eardrum permanently damaged in (1) a radical mastoid, and (2) a simple mastoid operation? Should a successful operation affect assessment for life assurance?*

A.—The eardrum is often removed in the radical mastoid operation, but modern tympanoplastic procedures endeavour to recreate an air-filled space containing the round window and eustachian tube after all the disease for which the original operation was done has been removed. In the simple cortical, or Schwartze, mastoid operation the eardrum and middle-ear structures are left intact, and the ear should be regarded as normal afterwards. For life assurance purposes both operations, if subsequent healing is complete, should not be regarded as a handicap. After a radical mastoid operation water should not be allowed to enter the cavity, and some medical examiners regard such an operation as a drawback so far as certain occupations, notably the armed Forces, are concerned.

Testosterone Replacement

Q.—*Sublabial methyltestosterone (50 mg. daily for 7 days, then 25 mg. daily for 14 days) has restored libido in a 40-year-old male. Does this dosage stimulate normal production of testosterone, or is it desirable to continue with a daily maintenance dose or with an intermittent dosage?*

A.—Methyltestosterone given in the way described cannot stimulate normal production of testosterone—it can only suppress it. The fact that the treatment has had such a definite result suggests that the patient was suffering from a true deficiency of testosterone. Therefore it may be supposed that continued maintenance therapy will be needed to prevent relapse. The correct dosage is the lowest which will suffice to retain the full benefits of testosterone therapy, and this can be judged only on clinical grounds. Most probably daily administration will be necessary.

Horn Player's Lip

Q.—*A French-horn player has a protruding lower lip, and pressure from the mouthpiece causes recurrent hardening, thickening, and peeling. He has no trouble on holidays. What treatment might help?*

A.—High-speed photography appears to have shown that when such an instrument is played the lower lip vibrates at a frequency of several hundred cycles per second. It is surprising that this does not always give rise to trouble. Presumably this patient's lip is somewhat more fleshy than the average and the trouble which arises is simply the result of this type of trauma. It is presumed that the lip returns to normal in the course of a week or two if the patient stops playing. I can suggest no way to prevent this happening except by limiting the amount of playing. The only treatment likely to help is rest and possibly the use of a bland application such as lanolin.

Smoked Foods and Carcinoma

Q.—*Is there any evidence of a connexion between smoked foods and carcinoma of the alimentary tract?*

A.—Although there is no clear-cut statistical evidence of a connexion between smoked food and cancer, it would seem possible that some forms of smoked food might involve a carcinogenic hazard. The use of old ships' timbers which have previously been treated with coal-tar for this purpose would seem to be particularly objectionable. The problem is one which needs further investigation.

Correction.—The last sentence of the summary in the article on diagnosis of chronic bronchitis by Dr. C. M. Fletcher and his colleagues (*Journal*, August 29, p. 257) should read: "Disability appears to be a more frequent consequence of chronic bronchitis in men than in women," and not "... a less frequent consequence."

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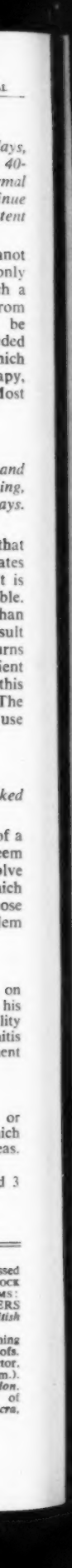
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